ORTHOGONAL FUNCTIONALIZATION STRATEGIES IN POLYMERIC MATERIALS

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ORTHOGONAL FUNCTIONALIZATION STRATEGIES IN POLYMERIC MATERIALS

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To my wife Hyunjung and my daughter Joanne

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LIST OF ABBREVIATIONS

A	hydrogen bonding acceptor
ATRP	atom transfer radical polymerization
^{13}C NMR	carbon magnetic resonance
^{o}C	degrees centigrade
cm^{-1}	wave number
CA	cyanuric acid
CT	chain terminator
CTA	chain-tansfer agent
CuAAC	copper-catalyzed azide-alkyne cycloaddition
δ	chemical shift
D	hydrogen bonding donor
DAN	diamidonaphthyridine
DAP	diamidopyridine
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCM	dichloromethane
DeAP	deazapterin
DLS	dynamic light scattering
DMAP	4-dimethylamino pyridine
DMF	*N*,*N*′-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DP	degree of polymerization

DSC	differential scanning calorimetry
EDCI	*N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimde
EWG	electron-withdrawing group
FT-IR	Fourier transform infrared
g	gram
GPC	gel-permeation chromatography
h	hour
^{1}H NMR	proton nuclear magnetic resonance
HPLC	high performance liquid chromatography
Hz	hertz
IR	infrared
ITC	isothermal titration calorimetry
J	coupling constant
Kcal	kilocalorie
K_a	association constant
K_d	dissociation constant
L	liter
M	molar
M^+	molecular ion
M^{-1}	inverse molar
m/z	mass-to-charge ratio
mg	milligram
min	minute
mL	milliliter
mmol	millimole

M_n	number-average molecular weight
mol	mole
MS	mass spectrometry
M_w	weight-average molecular weight
Napy	diamidonaphthyridine
NCN	nitrogen-carbon-nitrogen
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
PCC	pyridinium chlorochromate
PCP	phosphorus-carbon-phosphorus
PDI	polydispersity index
PEK	poly(etherketone)
PEO	poly(ethylene oxide)
PEG	poly(ethylene glycol)
PIB	poly(isobutylene)
PLA	poly(lactic acid)
PNB	poly(norbornene)
ppm	parts per million
RAFT	reversible addition-fragmentation chain-transfer
RNA	ribonucleic acid
rt	room temperature
ROMP	ring-opening metathesis polymerization
ROP	ring-opening polymerization
SCS	sulfur-carbon-sulfur

SABC	supramolecular alternating block copolymer
SHBC	supramolecular homoblock copolymer
STM	scanning tunneling microscopy
TBD	1,5,7-triazabicyclo-[4,4,0]-dec-5-en
T_g	glass transition temperature
THF	tetrahydrofuran
THY	thymine
UG	ureidoguanosine
UPy	ureidopyrimidinone
UV-VIS	ultraviolet-visible

SUMMARY

This thesis describes original research aimed at the development of highly efficient polymer functionalization strategies by introducing orthogonal chemistry within polymeric systems. The primary hypothesis of this thesis is that the use of click chemistries or noncovalent interactions can provide new and easy pathways towards the synthesis of highly functionalized polymers thereby addressing the shortcomings of traditional covalent functionalization approaches. To verify the hypothesis, the work presented in the following chapters of this thesis further explores previous methods of either covalent or noncovalent polymer functionalization described in Chapter 1.

Chapters 2 and 3 present advanced methods of covalent polymer functionalization based on high-yielding and orthogonal click reactions: 1,3-dipolar cycloaddition, hydrazone formation, and maleimide-thiol coupling. All three click reactions employed can be orthogonal to one another and conversions can be quantitative, leading to the easy and rapid synthesis of highly functionalized polymers without interference among functional handles along the polymer backbones.

The next two chapters focus on the noncovalent functionalization strategies for creating supramolecular block copolymers *via* the main-chain self-assembly of telechelic polymers. Novel synthetic methods to prepare telechelic polymers bearing terminal recognition motifs were developed through a combination of ROMP using functionalized ruthenium initiators and functionalized chain-terminators, and the resulting polymers were self-assembled to form supramolecular block copolymers. Chapter 4 demonstrates the formation of supramolecular multiblock copolymers *via* self-assembly of symmetrical

telechelic polymers using metal coordination, while Chapter 5 demonstrates that supramolecular ABC triblock copolymers can be prepared by the self-assembly of a heterotelechelic polymer as the central block with two other complementary monotelechelic polymers using two orthogonal hydrogen bonding interactions.

Chapter 6 presents a unique application of noncovalent functionalization approaches. The ultimate goal of this research is to develop a controlled polymerization method based on noncovalent templation. The initial attempts at the metal coordination-based template polymerization are presented in this chapter.

Finally, Chapter 7 summarizes the findings in each chapter and presents the potential extensions of the orthogonal functionalization strategies developed in this thesis.

CHAPTER 1

HIGH YIELDING FUNCTIONALIZATION STRATEGIES IN POLYMER SCIENCE

1.1 Abstract

This Chapter introduces highly efficient functionalization strategies in polymer science by dividing them into two categories: covalent and noncovalent strategies. Covalent strategies such as click chemistry are defined, while noncovalent functionalization strategies using supramolecular interactions, such as hydrogen bonding and metal coordination, are surveyed with distinction between side-chain and main-chain self-assembled polymers. An emphasis is placed on selective multifunctionalization, which is a prerequisite for a variety of future applications of polymeric materials.

1.2 Introduction

In nature, biological systems can undergo orthogonal chemical reactions, in which the coupling partners react selectively, without interference, between the diverse biological functionalities.[1,2] Examples of these orthogonal approaches include the recognition of a substrate by an enzyme, an antigen by an antibody, and a neurotransmitter by a neuroreceptor.[3-5] Nature's principles have been an inspiration for the chemical community to develop orthogonal functionalization strategies and to produce multifunctional polymeric materials. These functionalization strategies in polymeric materials fall into two main categories, either covalent or noncovalent functionalization.[6]

Over the past century, covalent approaches have been utilized to produce multifunctional polymers.[7] While highly successful, covalent functionalization methods are often cumbersome, time-consuming, and not quantitative, resulting in the formation of ill-defined polymeric materials. In order to overcome these challenges, polymer scientists have employed highly efficient covalent reactions which proceed in quantitative or nearly quantitative yields, without by-products, under mild reaction conditions, and are often referred to as click reactions.[8,9] Chapter 1.3 will define click chemistry in more detail and introduce its application to polymer science.

Noncovalent interactions have been introduced as a new concept in macromolecular systems in addition to click reactions to replace traditional covalent approaches, resulting in the foundation of supramolecular polymer science.[10] The combination of supramolecular interactions and synthetic polymers can improve the properties of polymeric materials.[10-12] In general, supramolecular polymers can be divided into two categories: side-chain and main-chain.[6,11,12] Side-chain supramolecular polymers are based on a covalent polymer backbone that contains molecular recognition units on the side-chains and can be functionalized *via* noncovalent interactions. In contrast, main-chain supramolecular polymers are defined as polymers that are held together by directional noncovalent interactions within the polymer backbone. Chapter 1.4 will describe current noncovalent approaches with distinction between side-chain and main-chain functionalized polymers.

1.3 Covalent Strategies

1.3.1 Click Chemistry

The term "click chemistry" was first introduced by K. Barry Sharpless, who defined click chemistry as a group of reactions that "*...must be modular, wide in scope, give very high yields, generate only inoffensive byproducts that can be removed by nonchromatographic methods, and be stereospecific (but not necessarily enantioselective). The required process characteristics include simple reaction conditions (ideally, the process should be insensitive to oxygen and water), readily available starting materials and reagents, the use of no solvent or a solvent that is benign (such as water) or easily removed, and simple product isolation. Purification, if required, must be by nonchromatographic methods, such as crystallization or distillation, and the product must be stable under physiological conditions*".[8] The most common examples that meet the criteria for click chemistry include the following classes of chemical transformations (Figure 1):

- Cycloadditions of unsaturated species. These primarily refer to 1,3-dipolar cycloaddition, but also include the Diels-Alder type transformation.[8,9]
- Nucleophilic substitution reactions. These refer to the ring-opening reactions of strained heterocyclic electrophiles such as epoxides, aziridines, aziridinium ions, cyclic sulfates, and episulfonium ions.[8,9]
- Carbonyl chemistry of the non-aldol type. Examples include the formations of ureas, thioureas, oxime ethers, hydrazones, amides, and aromatic heterocycles.[8,9] In general, carbonyl reactions of the aldol type have low

thermodynamic driving forces resulting in longer reaction time and by-product formation, and therefore cannot be considered as click reactions.[13]

- Additions to carbon-carbon multiple bonds. Examples include epoxidation, dihydroxylation, aziridination, sulfenyl halide addition, nitrosyl halide addition, and certain Michael additions.[8,9]

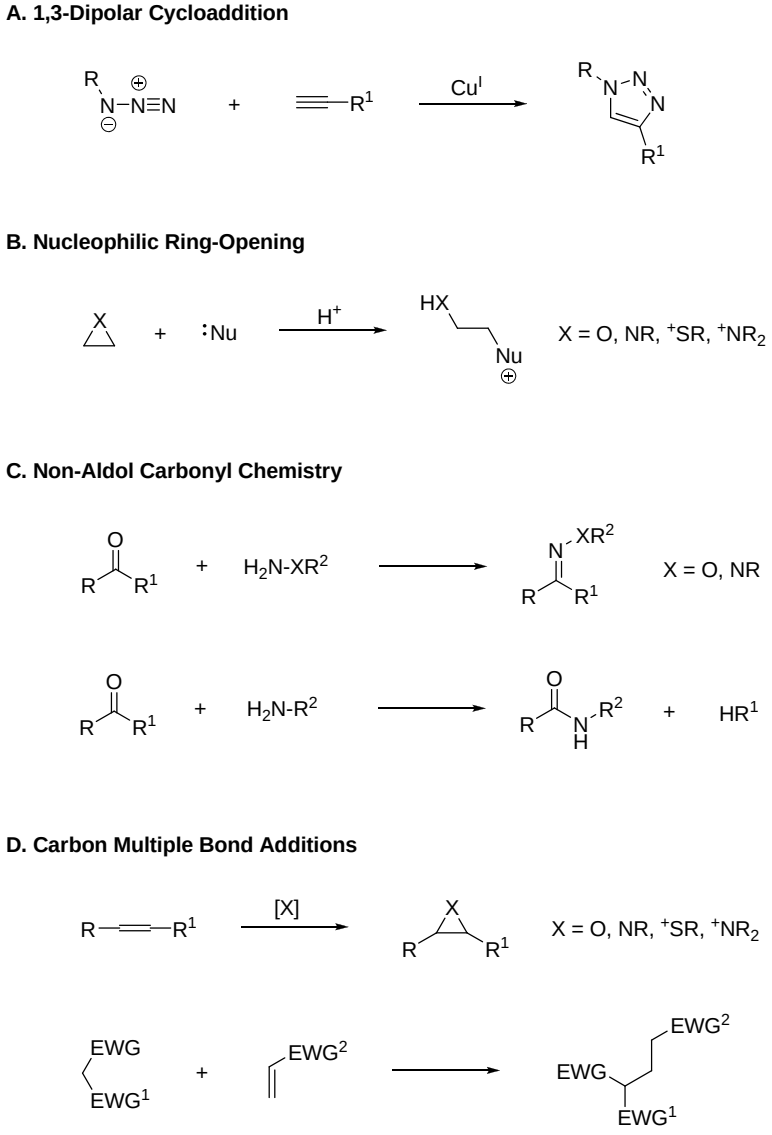


Figure 1.1. Major classifications of click reactions. Nu = nucleophile; EWG = electron-withdrawing group.[13]

Nevertheless, in the recent literature, the term "click chemistry" has been used almost exclusively to denote copper-catalyzed 1,3-dipolar azide-alkyne cycloadditions (Figure 1.1.A) among the four major classifications.[14-16] In this thesis, click chemistry is defined as a group of reactions that are fast, simple to use, easy to purify, versatile, regiospecific, and give high yields under mild reaction conditions.

1.3.2 1,3-Dipolar Cycloadditions

One of the most popular reactions within the click chemistry is the copper-catalyzed Huisgen azide-alkyne cycloadditions (CuAAC). The 1,3-dipolar cycloaddition of azides and alkynes to obtain 1,2,3-triazoles was first introduced by Arthur Michael in the late 19th century and was significantly developed by Rolf Huisgen in the 1960s.[17-19] In the absence of a transition-metal catalyst, these reactions are not regioselective and require high temperatures to give high yields (Figure 1.2.A).[16] In 2002, Meldal and co-workers reported that the use of a copper(I) catalyst that binds to terminal alkynes leads to highly efficient azide-alkyne cycloadditions at room temperature in organic media (Figure 1.2.B).[14,16] Shortly after, Sharpless and Fokin demonstrated that CuAAC can be achieved in polar media such as *tert*-butyl alcohol, ethanol, and water.[15] This CuAAC fulfills the click chemistry criteria perfectly, no matter how subjective they may be, and is therefore highly reliable and easy to use. This reaction is exclusively regiospecific by forming 1,4-substituted products in very high yields, and can be performed at room temperature, in a variety of solvents including water, over a wide range of pH values, and with rapid reaction rates.[13-15,20-26] These important features have led to applications in many areas, including bioconjugation, therapeutics, sugar-based materials, dendrimers,

fuctional polymers, and nanotube functionalization.[27-38] In particular, CuAAC has shown to be highly relevant for biological applications because it can be performed under reaction conditions that are compatible with biological environments - under aqueous conditions and at room temperature. In addition, azides are absent and alkyne functional groups are relatively rare in living systems, allowing for the chemoselective functionalization of biological systems.[16] For example, CuAAC has been investigated for designing a variety of biomaterials, such as stationary phases for bioseparation, drug delivery vehicles, site-specific modified proteins, protein or oligonucleotide microarrays, and functionalized cell surfaces.[16,39-46] The mandatory copper catalyst, however, is toxic to both bacterial and mammalian cells, thereby precluding applications wherein the cells must remain viable.[30,47]

An alternative, strain-promoted, cycloaddition strategy that avoids the use of the often toxic copper catalyst has been recently reported by Bertozzi and co-workers, who demonstrated that cyclooctynes readily undergo [3+2] cycloaddition with various azide derivatives under physiological conditions in the absence of auxiliary reagents (Figure 1.2.C).[47] They also demonstrated that this copper-free approach can be used for selective modification of biomolecules and living cells.[47-49] Using this approach, azide-modified human leukemic T cells could be functionalized with a biotin-containing cyclooctyne without any apparent toxicity; however, these cyclooctyne derivatives showed rather slow cycloaddition kinetics in comparison to CuAAC. To increase the sensitivity of the cyclooctynes for azide detection, electron-withdrawing groups were introduced on the α position of the triple bond.[48,49] Fluoro-substituents were chosen due to their synthetic accessibility and inertness in biological systems (Figure 1.2.D).[48,49] Although these

reactions are not regioselective, the strain-promoted and fluorine-activated cycloadditions have shown to be very fast and efficient and they exhibit some click features in the sense that they are chemoselective and readily applicable in physiological conditions. Importantly, these cycloadditions exhibit reaction kinetics comparable to those of CuAAC, allowing for important tools not only in chemical biology but also in some specific areas of materials science, where the use of copper catalyst is problematic.[16]

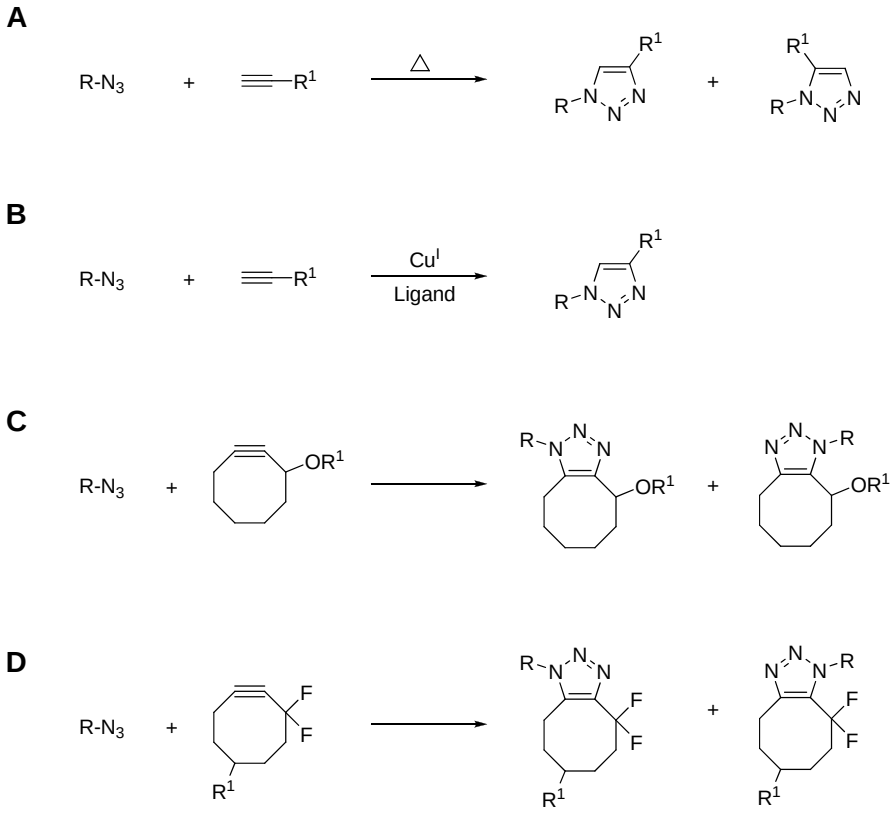


Figure 1.2. Different types of azide-alkyne cycloadditions. (A) Standard thermal cycloaddition; (B) copper-catalyzed cycloaddition; (C) strain-promoted cycloaddition; (D) strain-promoted and fluorine-activated cycloaddition.[16]

1.3.3. Aldehyde- and Ketone-Based Chemoselective Ligations

The demand for highly selective chemical reactions executable within the complex environment of a living organism has led chemists to explore chemoselective ligation techniques. First described by protein chemists, this refers to the coupling of two mutually and uniquely reactive functional groups in an aqueous environment[50] where these functional groups are selective for each other and also tolerate a diverse array of other functionalities, which can be termed as chemical orthogonality. Thus, chemoselective ligation reactions not only offer advantages similar to those of enzymatic reactions along with the potential of a wide range of substrates for use as coupling partners but also fulfill the click chemistry criteria.[51]

The most common examples of chemoselective ligation reactions use aldehydes and ketones as electrophiles that have a unique and selective reactivity with their complementary nucleophiles. For example, aldehydes and ketones react selectively with (i) hydrazides to form hydrazones (Figure 1.3.A), (ii) aminooxy groups to form oximes (Figure 1.3.B), and (iii) thiosemicarbazides to form thiosemicarbazones (Figure 1.3.C).[50] In addition, aldehydes can be readily coupled with β-amino thiols such as N-terminal cysteine residues to form thiazolidines (Figure 1.4.D).[50] It is important to note that although water is produced in these condensation reactions, the products are of sufficient thermodynamic stability under typical reaction conditions and the ligation reactions are favorable even in aqueous media.[50-53] These aldehyde- and ketone-based chemoselective ligation reactions have found widespread utility in the synthesis of highly functionalized macromolecules, in the conjugation of peptides, sugars, or drugs in specific orientations, and in the chemical remodeling of cell surfaces for biomedical applications.[54-59]

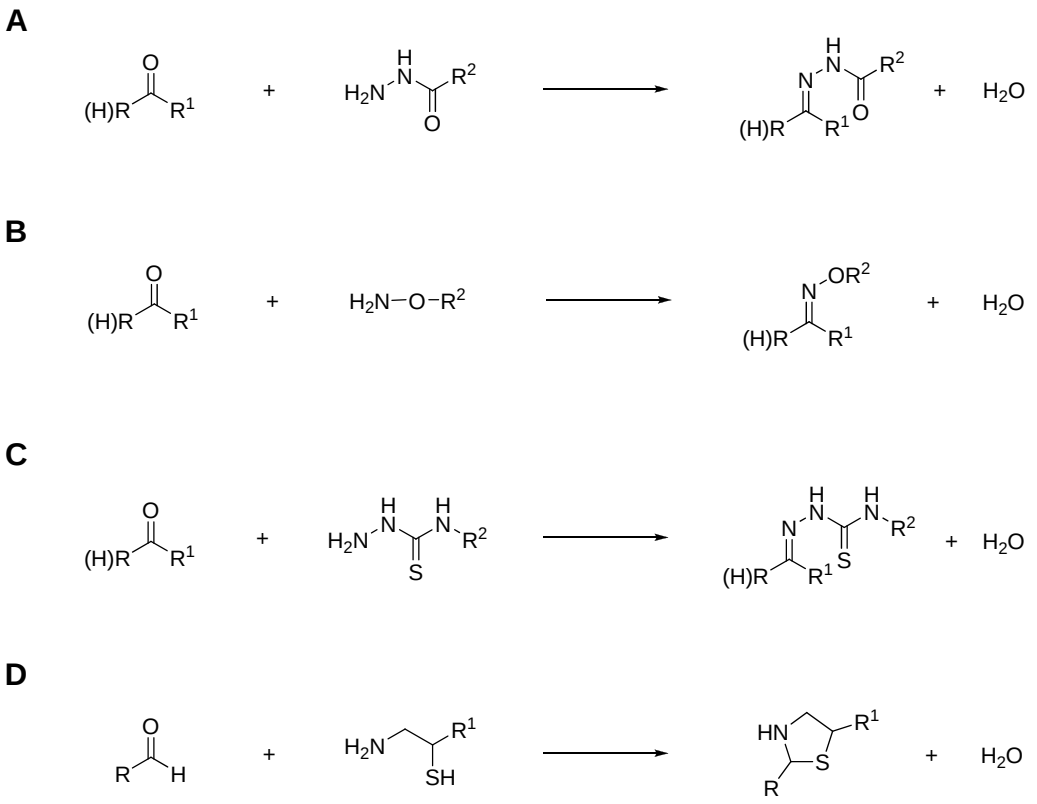


Figure 1.3. Examples of aldehyde- and ketone-based chemoselective ligation reactions.[50]

1.3.4. Thiol-Based Click Reactions

The thiol group is an extremely versatile handle for introducing functionalization, as it is capable of reacting with maleimides, iodoacetamides, alkenes, other thiols, and gold in high yields under mild reaction conditions (Figure 1.4).[60-65] These thiol-based ligation reactions also fulfill the click chemistry criteria. The coupling of thiols onto maleimides is a powerful means to conjugate two molecules (Figure 1.4.A). This reaction is rapid, highly selective, and essentially quantitative under physiological conditions, which makes it suitable for preparing an immunogen comprised of an antigen and a carrier molecule such as a protein.[66] In most proteins, the reaction sites are at cysteine

residues that are either intrinsically present or result from reduction of cystines. Unlike iodoacetamides, maleimide functionalities are highly selective for cysteine detection, as they do not react with tyrosines, histidines, or methionines under physiological conditions.[67,68] The maleimide-thiol coupling has been widely used for selective modification and conjugation of cysteine-containing biomolecules in bioconjugate chemistry, and thus maintains the acceptability for biological applications.[67,68]

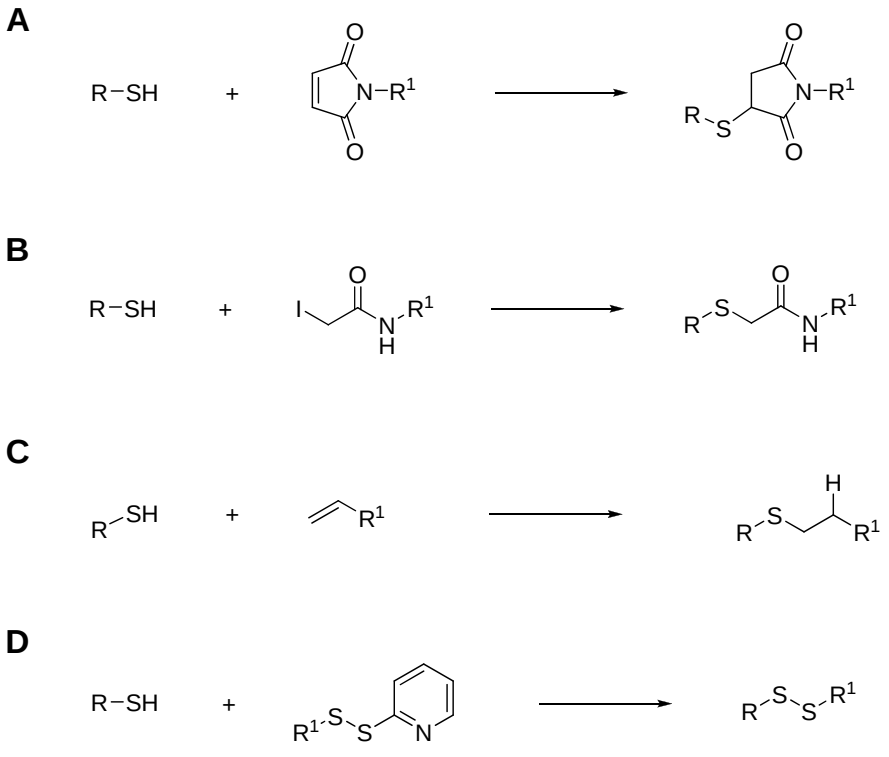


Figure 1.4. Examples of thiol-based click reactions.

1.3.5. Polymer Functionalization *via* Click Reactons

The synthesis of highly functionalized polymers is desirable since such polymers are potential materials for a variety of applications ranging from electronic devices to

biological materials.[69-74] These functional polymers can be synthesized by the direct polymerization of the desired functional monomers; however, many traditional polymerization techniques such as living anionic and cationic polymerizations have limited their use in the direct polymerization due to their inadequate functional group tolerance.[75] Although advances in controlled/living radical polymerization and catalytic polymerization techniques have improved the issue of functional group tolerance, there are still a number of functional groups that cannot be introduced by direct polymerization approaches using current polymerization techniques.[75]

Post-polymerization functionalization is an attractive strategy for the synthesis of highly functionalized polymers and can be used to overcome limited functional group tolerance. This approach is based on the polymerization of monomers possessing functional handles on the side-chains that are tolerant to the polymerization conditions but highly selective and reactive to undergo subsequent functionalization reactions with their complementary coupling partners bearing the desired functionalities. To afford well-defined functional polymers, this strategy requires highly efficient functionalization transformations that proceed quantitatively in an orthogonal fashion with high fidelity and selectivity under mild reaction conditions. This can be achieved by employing click reactions. Many research groups have utilized click reactions in the post-polymerization modification to create highly functionalized polymeric materials.[75] This section will focus on orthogonally multifunctionalized polymers using this strategy.

Kiessling and co-workers have synthesized poly(norbornene)-based block copolymers bearing reactive *N*-hydroxysuccinimidyl (NHS) esters and maleimides that can react with amines to form amides and with furans to form oxonorbornene

cycloadducts, respectively (Figure 1.5.A).[76] The bifunctional block copolymers were synthesized by the ring-opening metathesis polymerization (ROMP) of both norbornene-based monomers using Grubbs' 3rd generation initiator.[77] ROMP allowed for the functional group tolerance as well as control over the resulting polymer properties such as molecular weight and polydispersity. To test the Diels-Alder reaction of maleimides on the side-chains, they exposed the polymers to furan-functionalized poly(styrene) resin and found highly efficient polymer immobilization. The immobilized polymers that bear NHS esters on the other side-chains were further reacted with two amines containing a mannose derivative and 2,4-dinitrophenyl lysine, resulting in quantitative functionalization based on NHS ester disappearance. The authors demonstrated that the use of the two transformations, Diels-Alder reaction of maleimide with furan and NHS ester-based amidation, is effective for generating highly functionalized polymers in an orthogonal manner.

Hawker and co-workers reported the orthogonal approaches to both the cascade and the simultaneous functionalization of macromolecules using click reactions.[78] They combined copper-catalyzed 1,3-dipolar cycloaddition with other synthetic transformations such as activated ester-based esterification and amidation to obtain polyfunctional macromolecules in a one-pot process (Figure 1.5.B). Both, simultaneous and cascade functionalization strategies, were shown to be highly efficient, versatile, modular, and proceeded in quantitative yields with absolute fidelity and selectivity under mild reaction conditions. Their single-step strategies for generating multifunctional polymers represent a significant advance as compared to traditional multistep functionalization and the potential utility of click chemistry in materials chemistry.

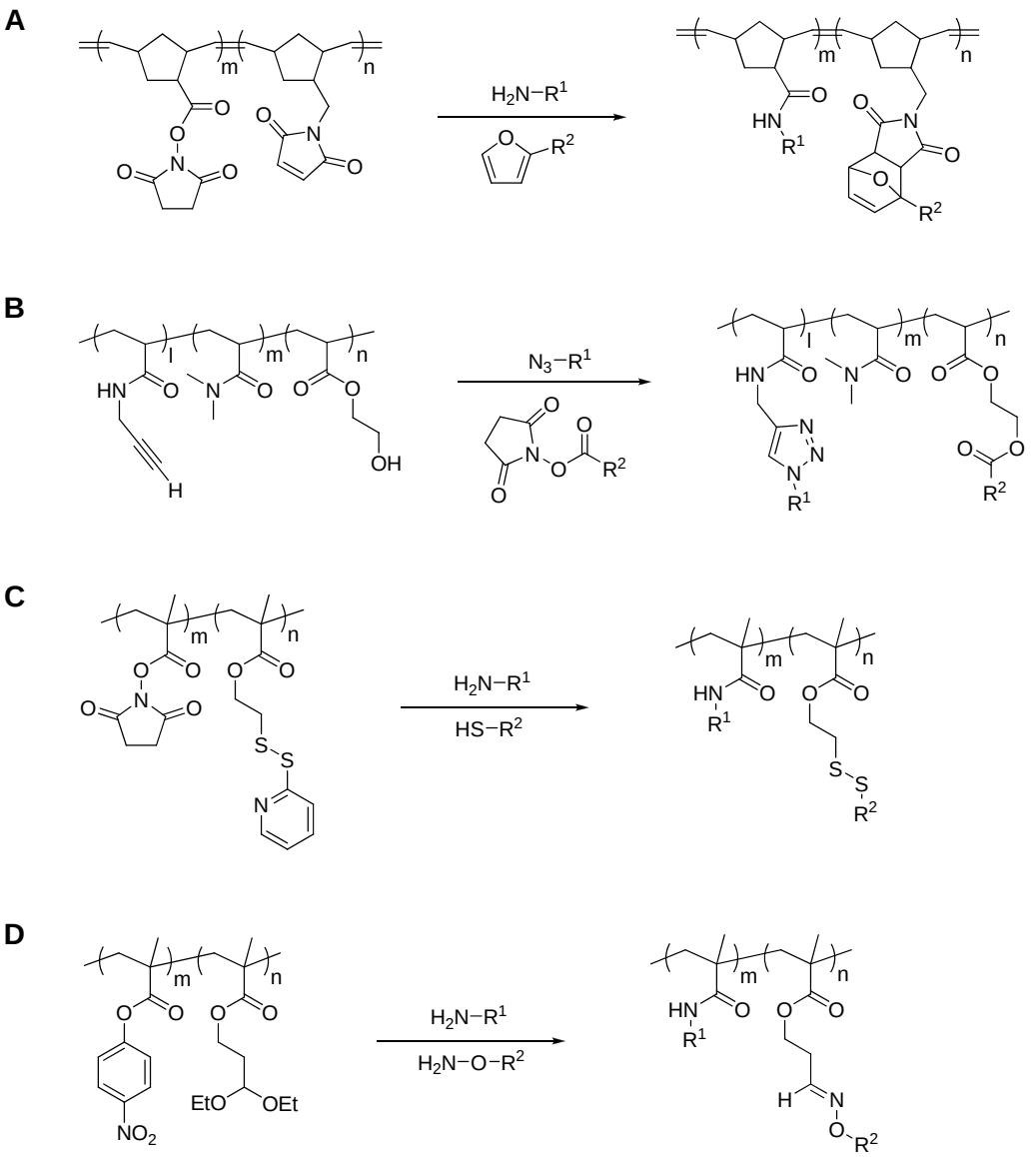


Figure 1.5. Examples of polymer functionalization *via* click reactions.

Disulfides are attractive functional groups that can react with thiol compounds of interest in high yields. Among these, pyridyldisulfide has been employed as a reactive functional handle on the polymer side-chains due to the fact that this reaction can be readily monitored by a characteristic UV/Vis absorption spectrum of the released 2-pyridinethione which is distinctly different from that of the pyridyldisulfide.[75,79]

Thayumanavan and co-workers have prepared copolymers bearing pyridyldisulfides and NHC esters that are complementary to thiols and amines, respectively, two of the most common reactive functionalities in biology (Figure 1.5.C).[80] They have shown that these polymers can be functionalized quantitatively either in a stepwise fashion or in one-pot using a mixture of reagents. Notably, they demonstrated that such polymers can be useful in biological applications including drug delivery, since the reversible disulfide linkage allows for the incorporation of biological molecules, such as drugs, followed by their release in a reducing environment.

Maynard and co-workers reported a reactive block copolymer scaffold that contains activated ester and protected aldehyde functional groups along the side-chains (Figure 1.5.D).[81] This block copolymer was synthesized by reversible addition-fragmentation chain-transfer (RAFT) polymerization[82] of both functional monomers *p*-nitophenyl methacrylate and diethoxypropyl methacrylate. The reactivity of the block copolymer was investigated by the stepwise functionalization of the side-chains. The activated ester block was first functionalized directly with allylamine which was chosen to provide a distinct signal by NMR spectroscopy. Subsequently, the resulting polymer was subjected to mildly acidic conditions to deprotect the acetal side-chains, forming aldehydes that were reacted with aminooxy compounds *in situ* to form oximes. ^{1}H NMR spectra revealed the allylamide and oxime formation in 75% and 89% yields, respectively. The authors demonstrated that this stepwise and selective functionalization strategy could be useful for generating multifunctional block copolymers for applications in drug delivery, gene therapy, nanotechnology, and combinatorial materials chemistry.

The research examples introduced herein demonstrate that click chemistry is a powerful tool for generating multifunctional polymeric materials. In all cases, activated ester-based esterification was employed as the functional handle and was combined with other transformations to obtain bifunctional copolymers in an orthogonal fashion. In order to construct more complex materials for a variety of future applications, the orthogonality of diverse synthetic transformations needs to be further explored. In this manner, we investigated the modularity and diversity of this strategy by combining different classes of click reactions for polymer functionalization. The details of these research accomplishments are surveyed in Chapters 2-3.

1.4 Noncovalent Strategies

1.4.1 Noncovalent Interactions

Nature utilizes a wide range of noncovalent interactions for the construction of biological macromolecules such as proteins, DNA, and RNA. The noncovalent interactions are reversible, selective, self-healing, and spontaneous, which allows for maintaining the three-dimensional structure of these biopolymers with a high degree of complexity. Based on the nature of the interaction, noncovalent interactions can be classified as hydrogen bonding, metal coordination, ionic and electrostatic interactions, van der Waals forces, π system interactions, and hydrophobic interactions. This section will introduce hydrogen bonding and metal coordination which are the noncovalent interactions employed in this thesis.

Hydrogen bonding, one of the most important interactions in biological systems, has been widely used in supramolecular polymer chemistry because of its synthetic

accessibility, directionality, and responsiveness towards a variety of external stimuli such as solvent, pH, and temperature.[11] In general, hydrogen bonding exists between a hydrogen atom that is covalently bound to an electronegative atom such as nitrogen, oxygen, or fluorine (hydrogen bond donor, D) and another electronegative atom (hydrogen bond acceptor, A). The strengths of single or double hydrogen bonds are highly influenced by the nature of donor and acceptor as well as solvent polarity, making them less useful for the preparation of complex macromolecular architectures.

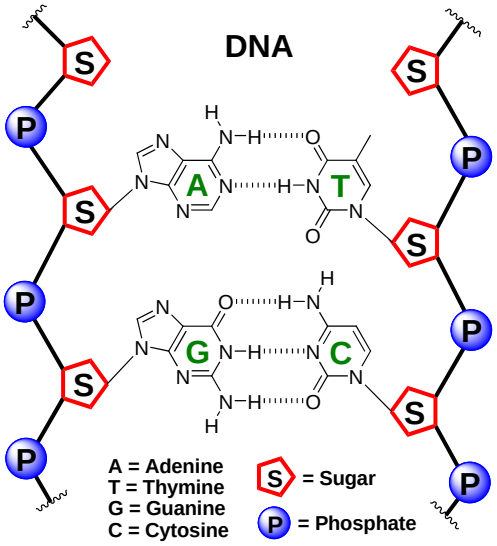


Figure 1.6. Hydrogen bonding within DNA.

The strength and specificity of hydrogen bonding can be enhanced by combining multiple hydrogen bonds in a unit and by employing a particular arrangement of the donor and acceptor sites, respectively.[83] The inspiration for this approach comes from nature (*e.g.* the nucleobase pairs of DNA). DNA consists of two strands of nucleotides that are held together by hydrogen bonding between their bases.[84] The complementary

base pair interactions between adenine and thymine or between guanine and cytosine are essentially responsible for stabilizing the double helical structure of DNA (Figure 1.6).

In supramolecular polymer chemistry, the majority of researchers utilize asymmetrical triple, quadruple, and larger hydrogen bonding motifs due to their significantly higher association constants that yield stable yet dynamic polymeric assemblies.[85-92] Figure 1.7 shows examples of the multiple hydrogen bonding pairs frequently used in supramolecular assemblies. The groups of Meijer and Zimmerman have developed self-complementary quadruple hydrogen bonding units, ureidopyrimidinone (UPy) and deazapterin (DeAP), respectively, that can also form very stable hydrogen-bonded heterocomplexes with diamidonaphthyridine (Napy/DAN) (Figure 1.7.A and B).[85-87] Although the self-complementary systems are excellent for the preparation of supramolecular polymers based on small molecules and cross-linked networks, they are less useful for the preparation of complex macromolecular architectures such as block copolymers, due to a lack of control of the self-assembly process. Researchers have therefore focused on non-self-complementary recognition pairs, such as the diamidopyridine-thymine (DAP-THY) complex (Figure 1.7.C), that exhibit only weak self-dimerization in nonpolar solvents (K_d < 50 M^{-1}).[83] Zimmerman and co-workers have recently reported an interesting non-self-complementary unit, ureidoguanosine (UG), which has a low tendency to self-associate and forms a highly stable complex with DAN ($K_a \sim 10^7$ M^{-1}) *via* quadruple hydrogen bonding arrays (Figure 1.7.D).[88-90] Another example of a non-self-complementary recognition pair is the sextuple hydrogen bonding array between diaminopyridine-substituted isophthalamide (often

referred to as the Hamiliton receptor or Wedge receptor) and either barbituric acid or cyanuric acid (CA) (Figure 1.7.E).[91,92]

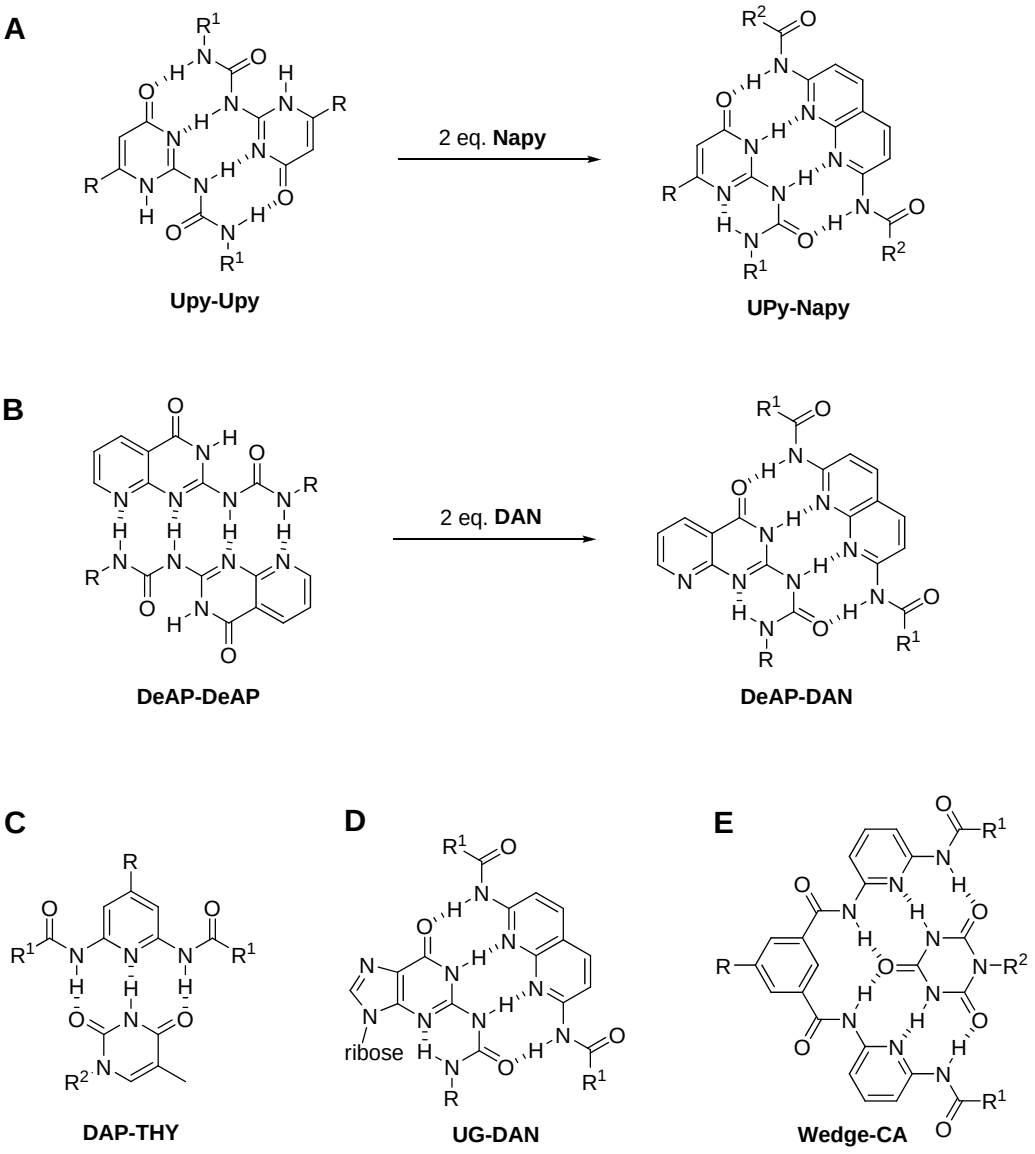


Figure 1.7. Complementary multiple hydrogen bonding pairs frequently used in supramolecular assemblies.

Another class of noncovalent interactions that has been used extensively in supramolecular chemistry is metal coordination. In many cases, metal coordination arises from the complexation of ligands with partial or full negative charges to metals with positive charges. The use of metal coordination is very promising for creating well-defined supramolecular polymeric assemblies because this interaction is highly directional as well as reversible. The most common examples of metal complexes used in supramolecular polymer chemistry include palladated pincers, bipyridines, and terpyridines (Figure 1.8)

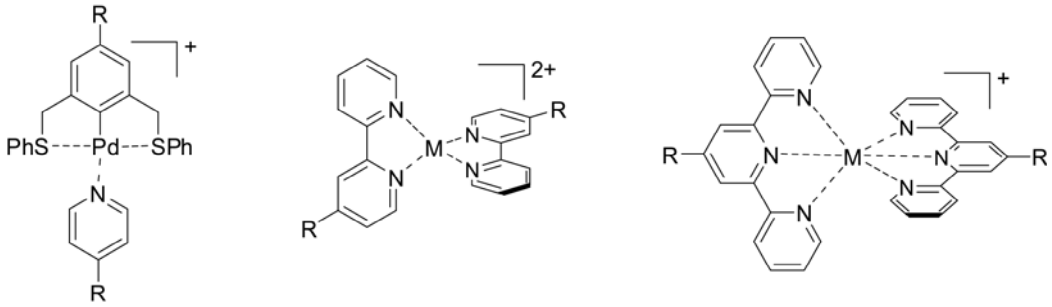


Figure 1.8. Well-known metal complexes based on chelating ligands.[93]

Pincer-type ligands have the general formula $[2,6\text{-}(ECH_2)_2C_6H_3]^-$ (ECE), where E represents a neutral two-electron donor and C is an anionic aryl carbon atom of the 2,6-disubstituted phenyl ring.[94] The pincer-type complexes commonly used in supramolecular chemistry are based on nitrogen-carbon-nitrogen (NCN), phosphorus-carbon-phosphorus (PCP), or sulfur-carbon-sulfur (SCS) ligands. Metal complexation with these pincer ligands usually affords the complexes [M(ECE)L] by forming two five-membered metallacycles (Figure 1.9).[94] In this thesis, the metal coordination system used

is based on a Pd(II) SCS pincer complex that is capable of binding pyridines, nitriles, and phosphines with high efficiency.[94,95] Pyridine-functionalized compounds were employed as the complementary ligands in this thesis because they can be complexed strongly to the metal with directionality but can be displaced easily by stronger coordinating phosphorus ligands.[95] Moreover, the pincer-pyridine self-assembly process can be readily characterized using ^{1}H NMR spectroscopy.

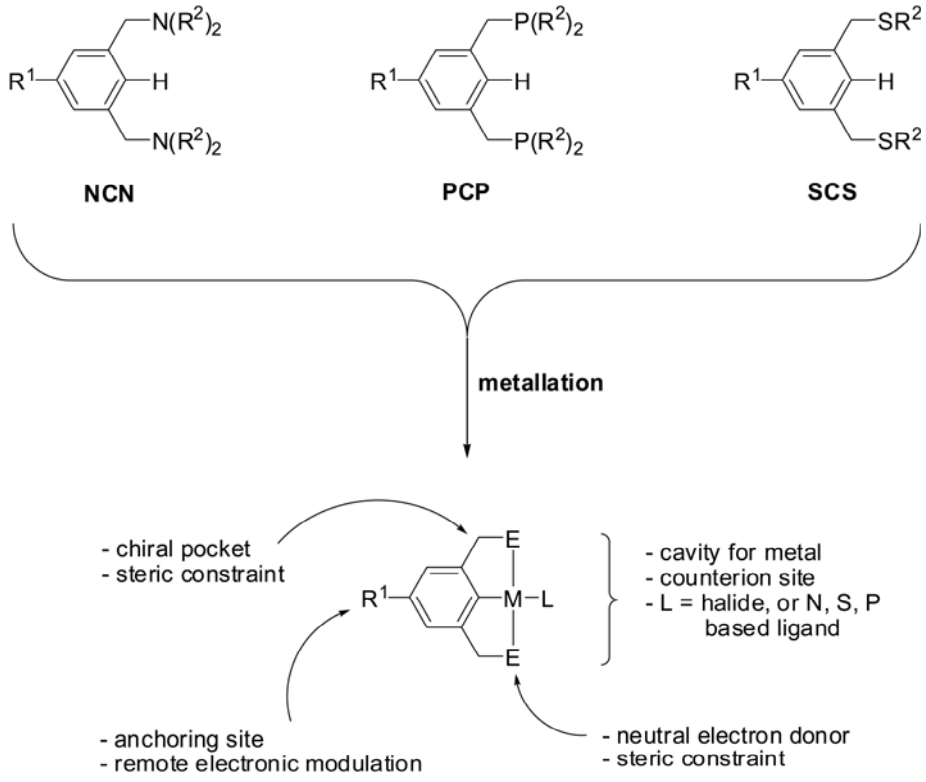
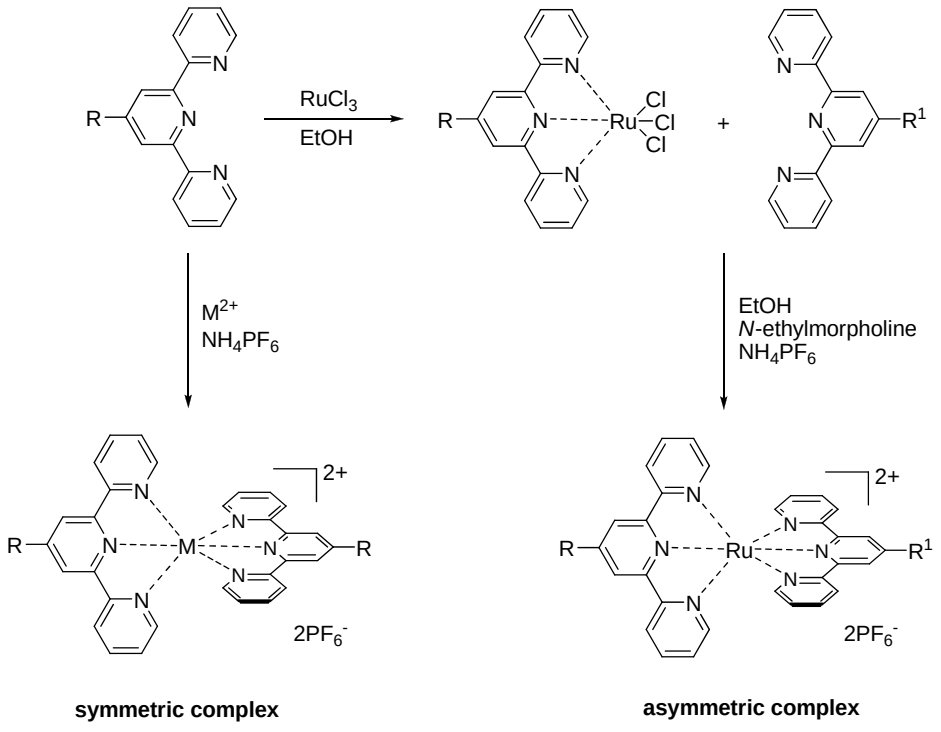


Figure 1.9. Pincer-type complexes.[94]

Multiple pyridine rings such as bipyridines and terpyridines are also very useful metal coordinating ligands since they allow for the reversible formation and cleavage of the metal complexes by external stimuli such as redox processes or competing ligand

additions.[93,96-97] Terpyridine-based ligands are more attractive for the preparation of well-defined supramolecular architectures, as 4'-functionalized bis-terpyridine complexes produce only single products without isomers. The binding strengths of the metal complexes highly depend on the metal ions used and therefore the supramolecular link can be tuned by adding the desired metal ions.[93] Moreover, both symmetric and asymmetric complexes can be easily prepared by taking, for example, advantage of ruthenium(III)/(II) chemistry (Scheme 1.1).[98] Therefore, the terpyridine-based ligands can be utilized as self-complementary as well as non-self-complementary recognition units.

Scheme1.1. Approaches to symmetric and asymmetric terpyridine metal complexes.[93]



symmetric complex **asymmetric complex**

1.4.2 Side-Chain Functionalized Supramolecular Polymers

The concept of side-chain supramolecular polymers utilizes noncovalent interactions such as hydrogen bonding and metal coordination in the modification of the side-chains along a polymer backbone to obtain highly functional polymeric materials with tailorable properties. This concept is based on nature's use of self-assembly in the creation of complex biopolymers such as DNA, RNA, and proteins and has the potential to overcome some of the drawbacks of current covalent functionalization strategies described earlier. Over the past decade, side-chain functionalized supramolecular polymers have been investigated extensively by many research groups.[6,12,115] Herein, some selected examples from the literature will be introduced with an emphasis on orthogonal multifunctionalization *via* hydrogen bonding and metal coordination.

Since the early work on the side-chain liquid crystalline polymers based on hydrogen bonding by Fréchet and Kato,[99-101] the research focus has moved to recognition motifs that are closely related to natural hydrogen bonding pairs. These recognition pairs such as thymine and diamidopyridine utilize three hydrogen bonds allowing for significantly strong noncovalent interactions. The group of Rotello has reported the hydrogen bonding-based functionalization of polymers containing triazine or diamidopyridine on the side-chains.[102-114] Using this noncovalent functionalization strategy named 'plug and play', they have synthesized a library of functional composite materials by self-assembling a variety of small molecules including flavin[102-107] and thymine derivatives[108] onto the polymers. Figure 1.10 describes the 'plug and play' strategy. This strategy was further expanded into nanoscience with the development of 'brick and mortar' self-assembly.[108-114] In this system, the diamidopyridine-functionalized

polymer (mortar) serves as glue between gold nanoparticles (bricks) containing complementary thymine receptors to direct the self-assembly.

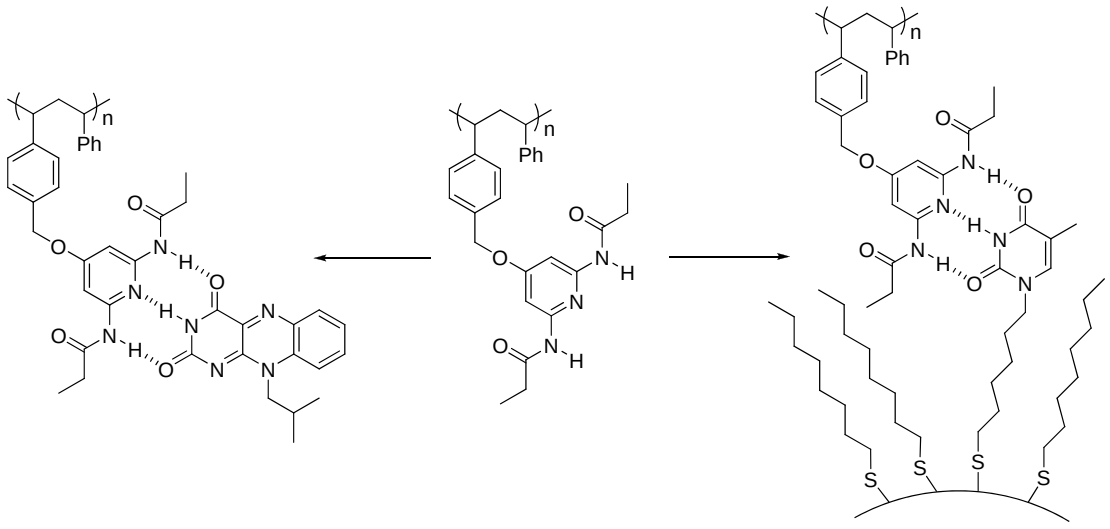


Figure 1.10. Self-assembly of diamidopyridine-functionalized polymers with flavin and thiolcoated gold nanoparticles.

In most cases, the Rotello group used poly(styrene) copolymers that required postpolymerization reactions due to the incompatibility of the recognition motifs with free radical polymerization methods to obtain the poly(styrene) backbones. This problem can be overcome by the use of highly controlled, living, and functional group tolerant polymerization methods such as ROMP, and these research efforts have been reported by the groups of Rotello, Sleiman, and Weck.[115-121] The Rotello group also synthesized rigid ROMP polymers bearing complementary diamidopyridine and uracil recognition units and investigated their self-assembly into spherical polymersomes that slowly fuse to form larger structures.[116] The Sleiman group employed ROMP to obtain adenine-functionalized copolymers that are able to fold into cylindrical morphologies resulting

from the self-complementary hydrogen bonding of the adenine units (Figure 1.11.A).[117,118] The Weck group investigated the effect of the hydrogen bonding moieties on the ROMP behavior of diamidopyridine- and diamidotriazine-functionalized norbornene monomers as well as the self-assembly of the resulting polymers with thymine-based molecules to create highly functionalized polymers (Figure 1.11.B).[121]

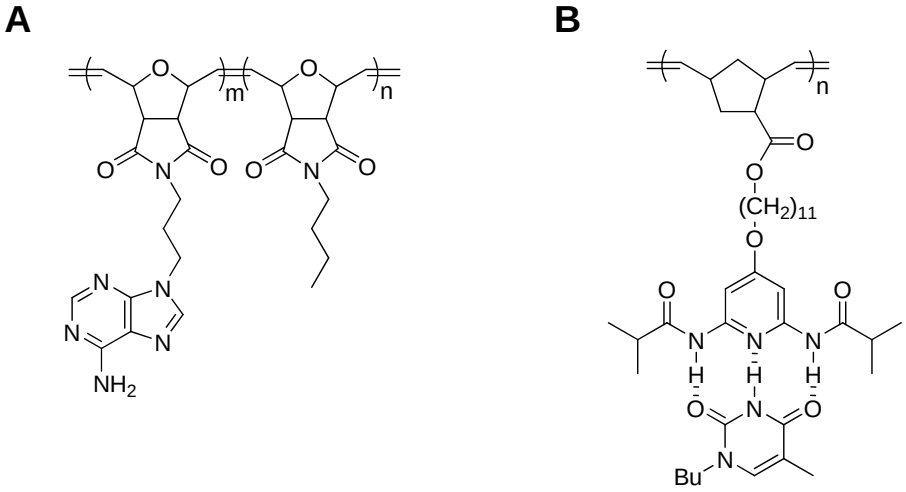
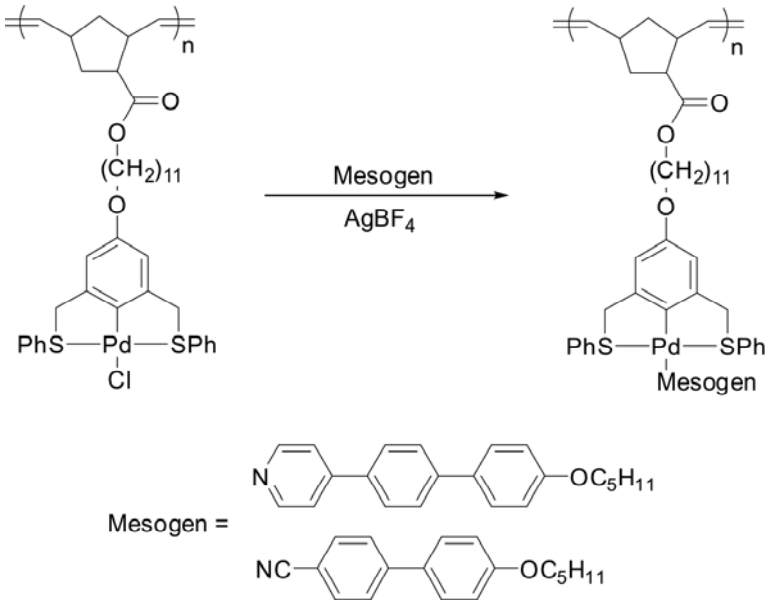


Figure 1.11. Adenine- (A) and diamidopyridine- (B) functionalized polymers prepared by ROMP.

In addition to hydrogen bonding, metal coordination has been used widely for supramolecular polymer functionalization.[122-127] Some of the major metal complexes employed as key components in side-chain supramolecular polymers are pincer-type complex. These complexes are particularly attractive due to their stable tridentate, square planar coordination spheres that possess only one open coordination site accessible for self-assembly.[94] The incorporation of pincer complexes onto polymers can lead to versatile and responsive materials *via* noncovalent side-chain functionalization. In 2002,

Weck and co-workers reported the first side-chain supramolecular polymer functionalized with pincer complexes.[120,123,124] The poly(norbornene)-based Pd(II) pincer complexes could be functionalized rapidly and quantitatively with a variety of complementary ligands including pyridines and nitriles, resulting in the formation of fully soluble and highly functionalized metal coordination polymers (Scheme 1.2).[124]

Scheme1.2. Functionalization of pincer-containing homopolymers.



While the previous examples describe that polymer modification can be accomplished *via* side-chain self-assembly by a single noncovalent interaction, either hydrogen bonding or metal coordination, the ultimate goal is to extend these methods to produce multifunctional polymeric architectures. Inspired by nature, which utilizes a variety of noncovalent interactions simultaneously to create vast libraries of biological materials in an orthogonal self-assembly process, a number of research groups have started to mimic nature's multifunctionalization strategy to produce complex

supramolecular structures.[6,115,128] For example, hydrogen bonding has been combined with metal coordination to synthesize dendrimers, self-organizing polymeric materials, and supramolecular main-chain polymers.[129-131] Such multifunctionalization strategies have also been used for the functionalization of side-chain supramolecular polymers. The combined use of metal coordination with hydrogen bonding as well as two distinct hydrogen bonding pairs have been reported by Weck and co-workers and the three examples will be discussed.[6,12,119,132-135]

First, random and block copolymers containing two different hydrogen bonding motifs, THY and CA, were synthesized by ROMP and then self-assembled with the complementary DAP and Hamilton receptors, respectively.[133] The selective multifunctionalization of the copolymers was accomplished *via* a one-step orthogonal self-assembly in the presence of competitive recognition sites (Figure 1.12.A). The second example utilizes two unique types of noncovalent interactions that would not interfere with each other, such as metal coordination and hydrogen bonding. The Weck group demonstrated that Pd(II) pincer complex- and DAP-functionalized copolymers could be functionalized with pyridine and THY, respectively, by both stepwise and one-step, orthogonal self-assembly (Figure 1.12.B).[132] Afterward, this orthogonal multifunctionalization strategy was expanded to functionalize terpolymers using a combination of metal coordination, hydrogen bonding, and pseudorotaxane formation.[136] The orthogonal and stepwise functionalization of the terpolymers was achieved by self-assembling pyridines to the Pd(II) pincer complexes, dibenzylammonium ions to the dibenzo[24]crown-8 rings, and THY to the DAP receptors (Figure 1.12.C). These multifunctionalization strategies developed by the Weck group potentially allow for the

synthesis of vast libraries of materials, thereby facilitating rapid optimization of polymeric materials.

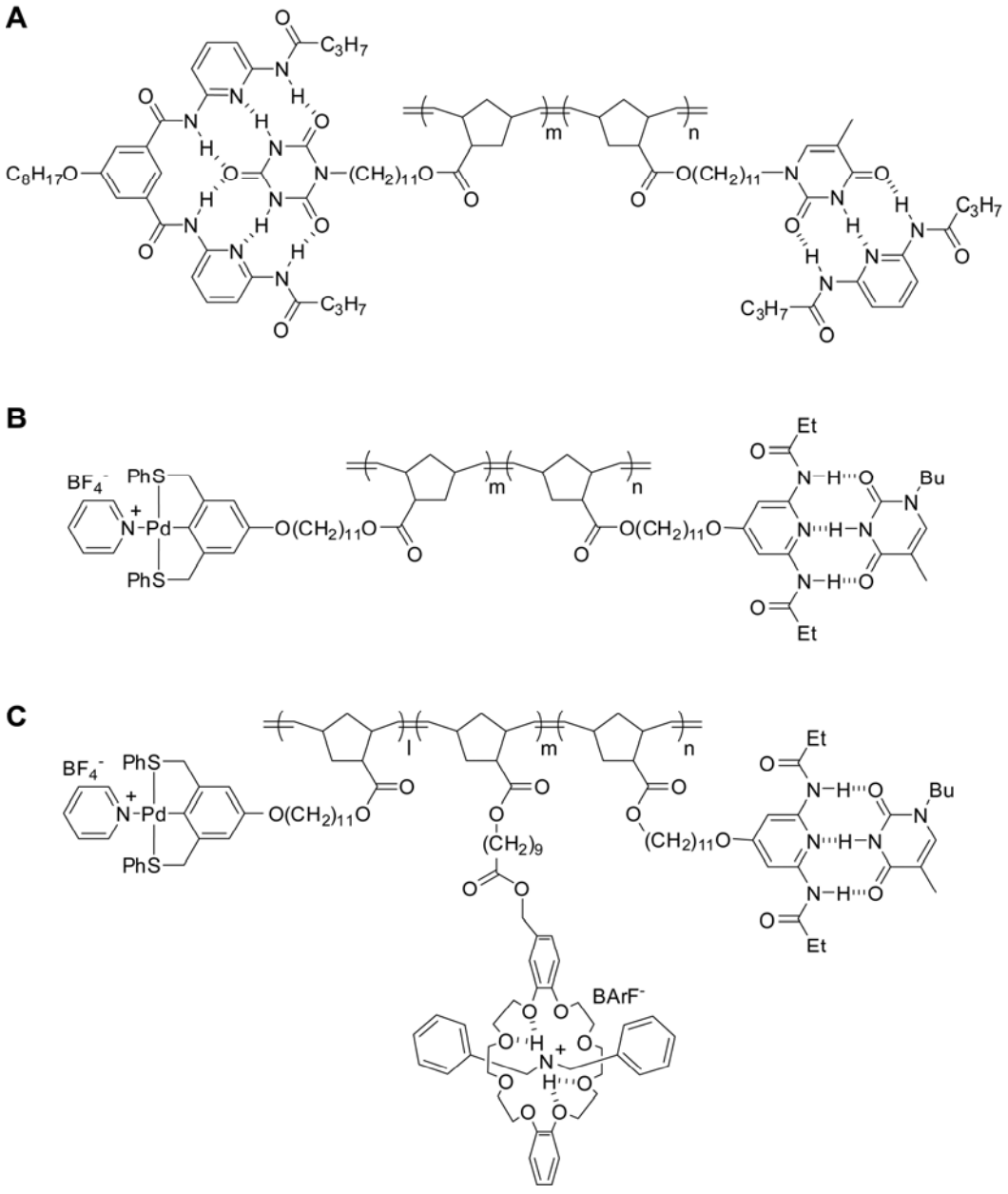


Figure 1.12. Side-chain functionalized copolymers containing recognition moieties along the polymer backbones.

1.4.3 Main-Chain Functionalized Supramolecular Polymers

Main-chain supramolecular polymers can be described as polymers that are held together by directional noncovalent interactions within the polymer backbone. The introduction of noncovalent interactions such as hydrogen bonding and metal coordination between polymeric constituents allows for the modular construction of well-defined supramolecular polymeric assemblies including supramolecular block copolymers, which are of considerable interest due to their promise in a wide range of applications as they combine the phase separation behavior of block copolymers with the responsiveness of supramolecular polymers.[137-148] A simple method for the formation of supramolecular block copolymers is the self-assembly of complementary supramolecular telechelic polymers. A telechelic polymer is a polymer containing one or more functional groups at the polymer chain-ends. When the functional end groups are noncovalent recognition units that can undergo self-assembly, the polymer can be defined as a supramolecular telechelic polymer. Supramolecular block copolymers can be mainly categorized into AB diblock and $(AB)_n$ multiblock copolymers. While a monotelechelic polymer, A, can self-assemble with another monotelechelic polymer, B, containing a recognition end unit complementary to that of A to form an AB diblock copolymer (Figure 1.13.A), $(AB)_n$ multiblock copolymers can be obtained by self-assembling two symmetrically end-functionalized polymers A and B (Figure 1.13.B). Herein, some selected literature examples of supramolecular block copolymers prepared by main-chain functionalization will be introduced with distinction between AB diblock and $(AB)_n$ multiblock copolymers.

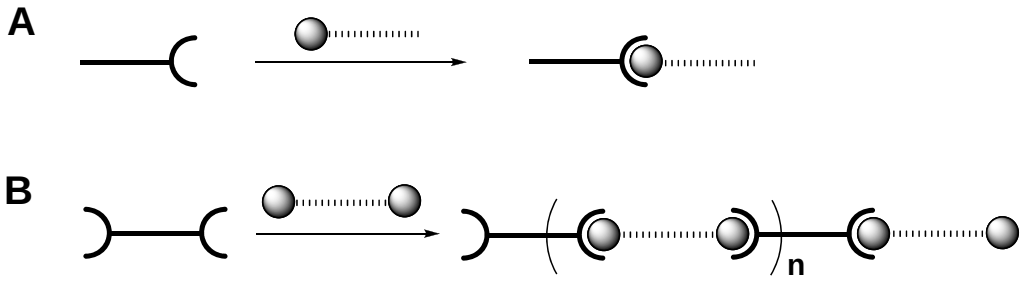


Figure 1.13. Schematic representation of the synthetic strategies towards supramolecular AB diblock and $(AB)_n$ multiblock copolymers.

Supramolecular AB Diblock Copolymers

Metal coordination units have often been used for the construction of supramolecular AB diblock copolymers due to their high association constants and directionality.[149-151] The Schubert group has synthesized terpyridine-functionalized monotelechelic polymers that can form stable bis-complexes with a variety of transition metal ions.[149,150] In particular, asymmetric complexes could be obtained by the addition of ruthenium, allowing for the preparation of a library of metallo-supramolecular AB block copolymers based on two different blocks, poly(styrene) and poly(ethylene oxide) (Figure 1.14). The reversibility was demonstrated by preparing micelles of the amphiphilic supramolecular block copolymers held together by a ruthenium(II) terpyridine connection. Upon treatment of the micelles with an excess of a strong competing ligand, the red color of the ruthenium complexes disappeared and the size of the micelles became smaller, indicating cleavage of the water-soluble block. The authors demonstrated that the reversibility of the supramolecular connections opens up avenues for the construction of switchable materials.

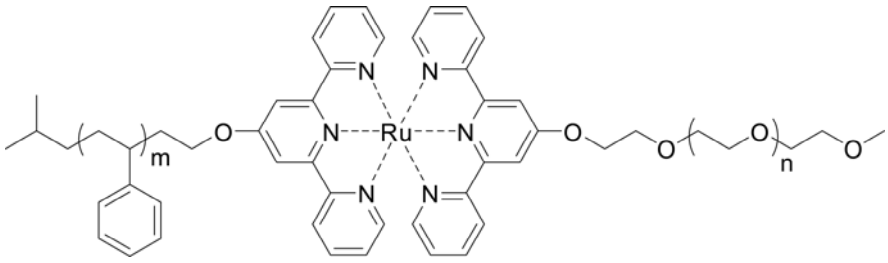


Figure 1.14. Metallo-supramolecular PS-[Ru]-PEO block copolymer.

Another example of supramolecular AB diblock copolymers is based on pincer-pyridine metal coordination. O'Reilly and co-workers afforded unsymmetrical amphiphilic metallo-diblock copolymers by self-assembling Pd(II) SCS pincer ligand-functionalized poly(acrylic acid) block with a pyridine end-functionalized poly(styrene) block (Figure 1.15).[151] The resulting diblock copolymers were further self-assembled to form well-defined, monodisperse micelles and nanoparticles. From the noncovalently connected nanoparticles, hollow cage-like structures with well-defined interior functionalities could be prepared by removing the hydrophobic core domain via dialysis at low pH. The authors demonstrated that these metal-functionalized hydrophilic nanocages are ineffective in the sequestration of hydrophobic guest molecules relative to the parent nanoparticle and the metal centers within the nanostructures have potential in pseudo-homogeneous supported Heck coupling reactions.

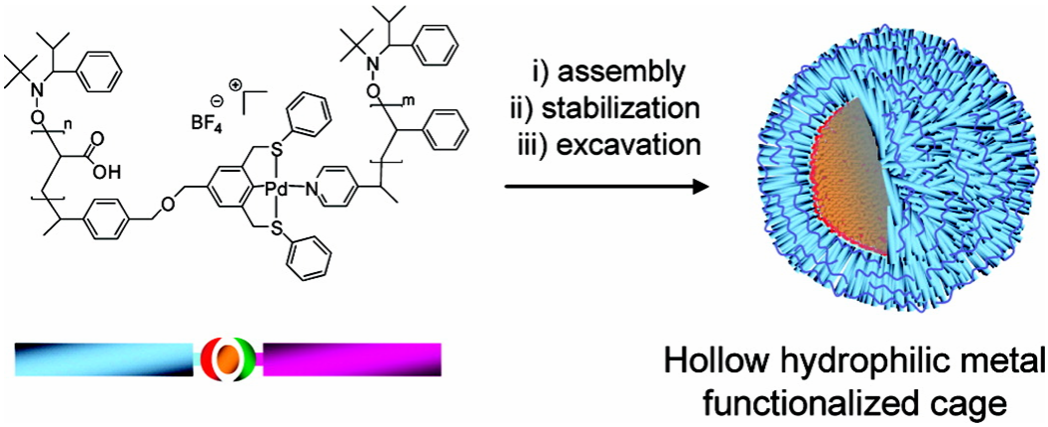


Figure 1.15. Amphiphilic diblock copolymer and metal-functionalized nanocages (Adapted image).[151]

The Hawker and Meijer groups have also obtained AB diblock copolymers *via* the self-assembly of (meth)acrylic polymers functionalized with the multiple hydrogen bonding functionalities, UPy and Napy, at the chain-end and studied the relationship between the end group structures and physical properties (Figure 1.16).[152] The bulk blending studies revealed that the phase behavior can be controlled by the specificity of the hydrogen bonding units present in the blend. For example, complementary UPy-Napy interactions resulted in a dramatic retardation of phase separation, while self-complementary UPy-UPy groups led to a slight compatibilizatioin. The authors also demonstrated that blending of UPy-functionalized benzyl methacrylate and Napy-functionalized *n*-butyl acrylate homopolymers allowed for a significantly stable nanostructured material, suggesting the dynamic presence of some amount of supramolecular diblock copolymers at the blend interfaces.

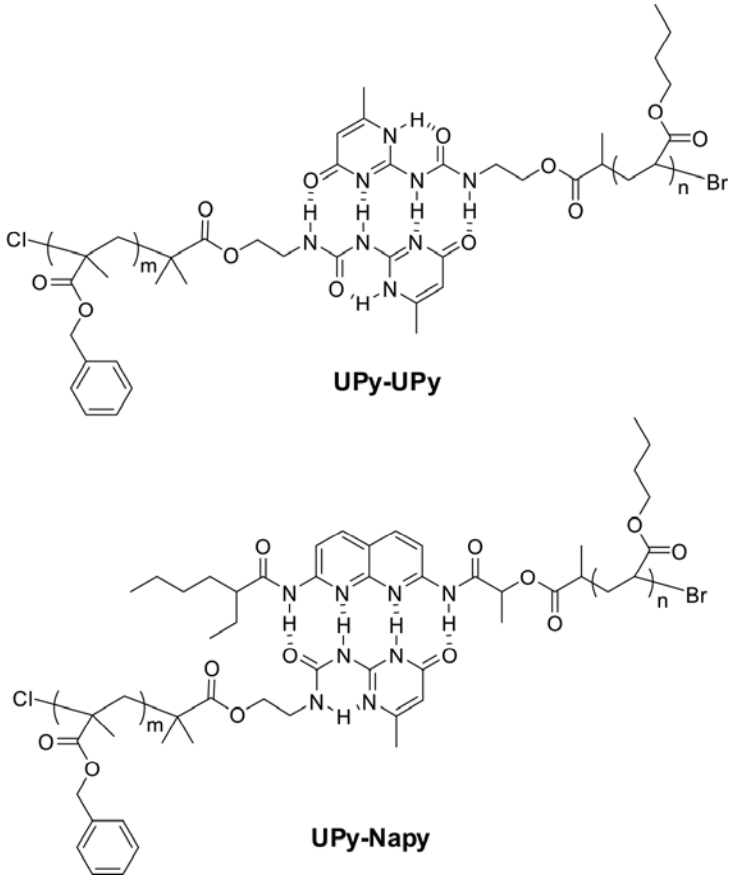


Figure 1.16. Hydrogen-bonded AB diblock copolymers.

Supramolecular $(AB)_n$ Multiblock Copolymers

Multiblock copolymers are of particular interest since unprecedented polymeric blends with tunable physical properties can be obtained easily by mixing two appropriately functionalized homopolymers.[153-154,158,159] Noncovalent interactions such as hydrogen bonding and metal coordination have been used to form multiblock copolymers. For example, the group of Binder reported the synthesis of telechelic poly(isobutylene)s (PIBs) functionalized with thymine or the Hamilton receptor and poly(etherketone)s (PEKs) functionalized with triazine or barbituric acid at both polymer chain-ends (Figure

1.17).[153] By combining the two strongly phase-separating polymers (PIBs and PEKs) *via* complementary hydrogen bonding, they obtained pseudo multiblock copolymers and studied the thermal behavior of the polymers. The weaker thymine-triazine hydrogen bonding could stabilize the microphase-separated material up to temperatures corresponding to the T_g of the PEK component, while the stronger interactions between the Hamilton receptor and barbituric acid led to the stabilization up to 80 °C above the T_g of the PEK. This dynamic feature demonstrates that the methods can be useful for creating materials with a variety of tunable properties.

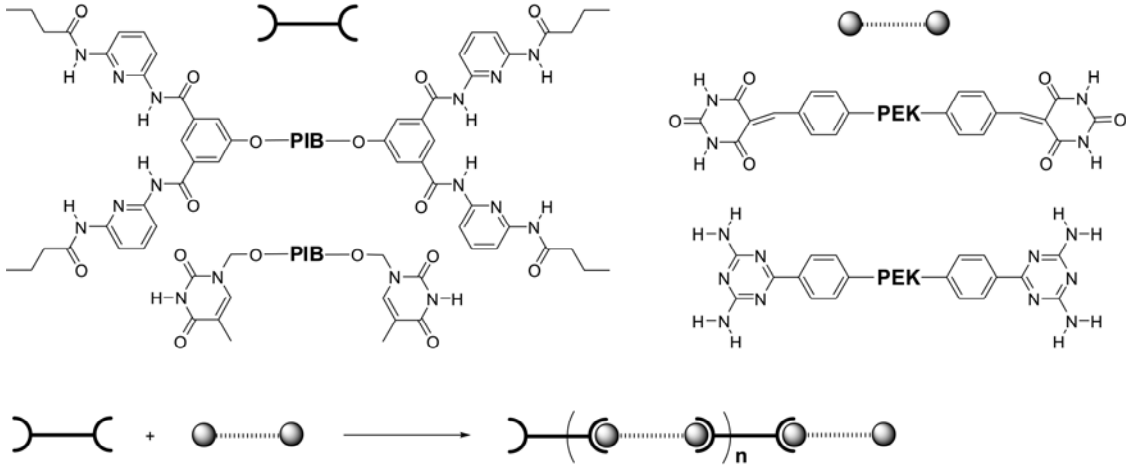


Figure 1.17. Self-assembly of telechelic polymers into supramolecular multiblock copolymers. PIB = poly(isobutylene); PEK = poly(etherketone).

Zimmerman and co-workers have recently developed a non-self-complementary hydrogen bonding motif, UG, which forms a highly stable complex with DAN ($K_a \sim 10^7$ M^{-1}) *via* quadruple hydrogen bonding arrays.[88-90] They prepared hydrogen-bonded multiblock copolymers in solution based on the UG-DAN interactions in which the

degree of polymerization could be tuned by the concentration and ratio of the blocks in the mixture (Figure 1.18).[154] Furthermore, the thermo-reversible property of these multiblock copolymers was demonstrated.

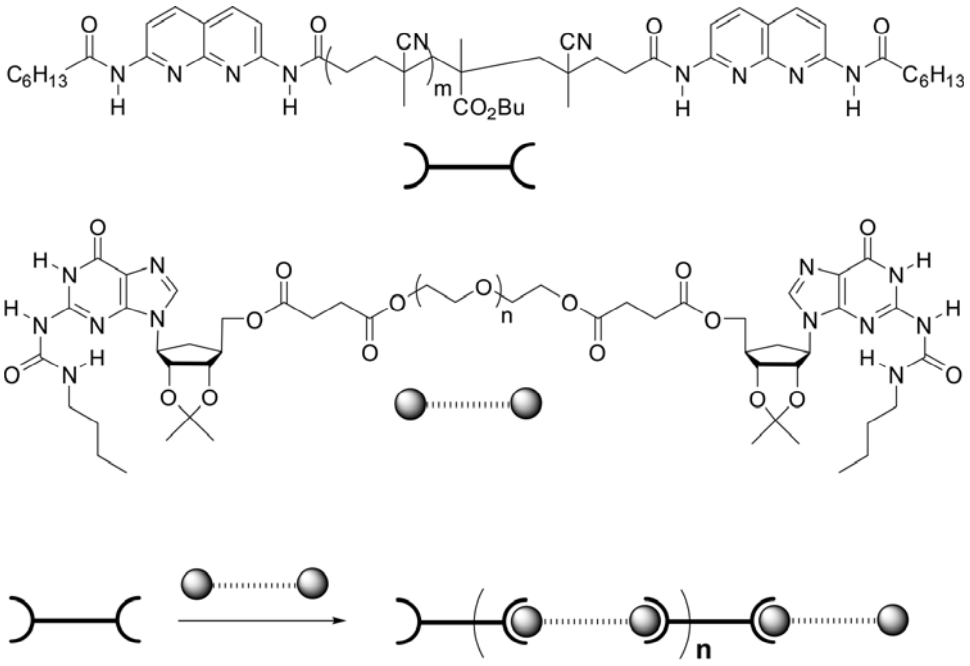


Figure 1.18. Self-assembly of telechelic polymers into supramolecular multiblock copolymers.

Most synthetic strategies towards multiblock copolymers, including the above examples, rely on post-polymerization functionalization steps to introduce the molecular recognition moiety, often resulting in nonquantitative conversions and requiring reaction conditions that may be incompatible with other functionalities along the polymer. The successful synthesis of telechelic polymers with complementary binding motifs that circumvents the need for post-polymerization functionalization is a desirable prerequisite for the easy and high-yielding preparation of well-defined supramolecular block

copolymers. The ROMP of cyclic olefins in the presence of bi-functional chain-transfer agents (CTA) is an efficient strategy for the incorporation of supramolecular functionalities onto both chain-ends of a polymer.[155-157] The group of Weck employed this methodology to introduce hydrogen bonding and metal coordination moieties at polymer chain-ends, allowing for the complete incorporation of the recognition units *in situ* (Figure 1.19).[158] The resulting telechelic polymers were self-assembled into supramolecular multiblock copolymers *via* hydrogen bonding or metal coordination between corresponding terminal recognition units.

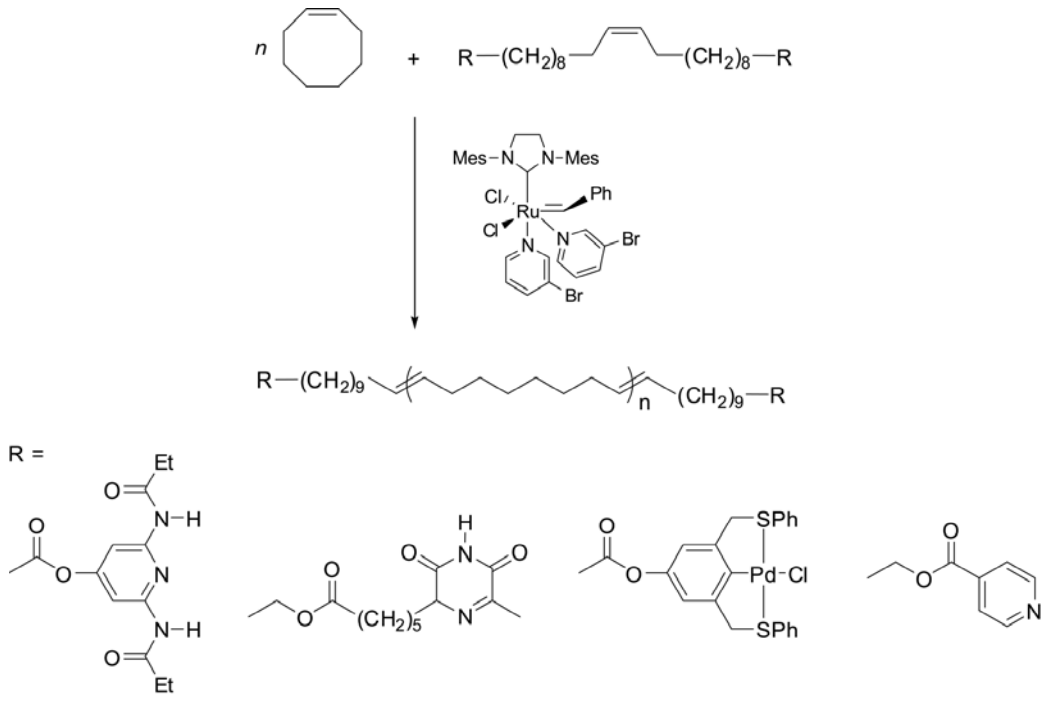


Figure 1.19. Synthesis of telechelic polymers by ROMP in the presence of functionalized CTAs.

Meijer and co-workers also synthesized bifunctional telechelic polymers through ROMP in the presence of CTAs functionalized with complementary quadruple hydrogen bonding motifs, UPy and Napy (Figure 1.20).[159] The formation of multiblock copolymers was demonstrated by self-assembling the resulting telechelic polymers in both solution and the bulk, leading to stable, microphase-separated copolymer morphologies.

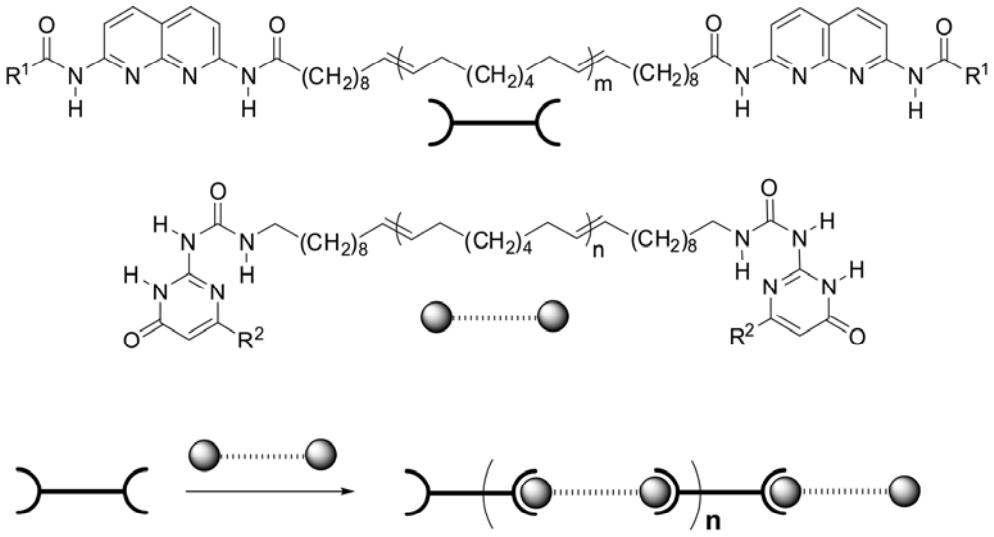


Figure 1.20. Self-assembly of telechelic polymers into supramolecular multiblock copolymers.

The research efforts described in this section demonstrate the potential of noncovalent functionalization strategies in the generation of complex supramolecular polymeric materials and in the tuning of bulk polymer properties such as morphology and processability. Furthermore, the combination of different, distinct, and orthogonal supramolecular interactions within polymeric systems will open a pathway for the preparation of a new class of materials with unique properties.

1.5 Conclusion

Post-polymerization functionalization is an attractive approach for the synthesis of functional polymers that overcomes the limited functional group tolerance of a number of polymerization methods. The success of this approach requires quantitative, selective, and functional group tolerant transformations. This chapter has surveyed two different classes of strategies for obtaining highly functionalized polymers. The first strategy is based on covalent synthetic chemistry using click reactions, including 1,3-dipolar cycloadditions and aldehyde-, ketone-, and thiol-based ligations that are fast, regiospecific, and give high yields under mild reaction conditions. Noncovalent interactions, such as hydrogen bonding and metal coordination, can also be used for the side- and main-chain modification of supramolecular polymers in a highly controlled fashion. The incorporation of supramolecular interactions can improve the versatility of polymeric materials, thereby generating dynamic and reversible 'smart' materials. The two strategies have shown to be excellent tools for polymer functionalization by overcoming some of the drawbacks of traditional covalent polymer synthesis including nonquantitative conversions and lengthy syntheses.

This thesis primarily aims to further explore the functionalization strategies described in this chapter to obtain multifunctional polymeric materials, with the development of selective chemistry that is orthogonal to the diverse functional groups present in polymeric systems. The motivation for the research in this thesis lies in nature's multifunctionalization strategy for creating vast libraries of biological materials with a high degree of complexity. The major research achievements that rely on either

covalent or noncovalent strategies will be addressed with an emphasis on orthogonal functionalization in the following chapters.

Chapters 2 and 3 present research focused on advancing the covalent functionalization strategies through click reactions. The goal of this research is primarily to develop a methodology for the efficient and high-yielding polymer multifunctionalization by combining different and orthogonal transformations. Chapter 2 first presents a library of modular functionalizations of the azide- and ketone-containing copolymers that involves (i) a single orthogonal functionalization *via* either 1,3-dipolar cycloaddition or hydrazone formation and (ii) a one-pot dual functionalization using both transformations simultaneously. In Chapter 3, this orthogonal functionalization strategy is further expanded to functionalize terpolymers using a combination of 1,3-dipolar cycloaddition, hydrazone formation, and maleimide-thiol coupling. These chapters demonstrate that all investigated transformations can be orthogonal and quantitative, allowing for the efficient synthesis of highly functionalized polymeric materials.

Chapters 4 and 5 focus on the main-chain functionalization strategies for creating supramolecular block copolymers through noncovalent interactions such as hydrogen bonding and metal coordination. Chapter 4 presents a methodology for the synthesis of symmetrical telechelic polymers bearing terminal recognition motifs *via* ROMP using a bimetallic ruthenium initiator and functionalized chain-terminators. This chapter demonstrates that the combination of a living/controlled polymerization method with metal coordination-based self-assembly allows for the formation of well-defined supramolecular alternating multiblock copolymers. Chapter 5 presents the synthesis of heterotelechelic polymers possessing two different recognition units at the chain-ends

which is a key step for the preparation of supramolecular ABC triblock copolymers. This chapter further demonstrates both the stepwise and one-pot formation of supramolecular ABC triblock copolymers *via* main-chain self-assembly of telechelic polymers using two distinct and orthogonal recognition events.

Chapter 6 presents a unique application of noncovalent functionalization approaches in the creation of well-defined polymeric materials. The goal of this research is ultimately to develop a controlled polymerization method by mimicking nature's templation strategies to produce biopolymers with controlled lengths, tacticities, and sequences. The initial attempts at the template-assisted polymer synthesis that utilize metal coordination to attach monomers to the polymeric template are presented in this chapter.

Finally, Chapter 7 summarizes the main conclusions of each chapter and presents the potential extensions of the orthogonal functionalization strategies developed in this thesis.

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CHAPTER 2

FUNCTIONALIZATION OF RANDOM COPOLYMERS THROUGH CLICK REACTIONS

2.1 Abstract

Poly(norbornene)-based random copolymers possessing an azide along with either an aldehyde or ketone functionality on each repeating unit were synthesized using ring-opening metathesis polymerization. The orthogonal functionalization of the resulting copolymers using 1,3-dipolar cycloadditions and hydrazone formations was investigated. While the azide- and aldehyde-containing copolymers were insoluble in organic solvents, the azide- and ketone-functionalized copolymers were fully soluble in common solvents such as CH_2Cl_2, THF, and DMF and can be quantitatively functionalized with a library of small organic and biological molecules in a step-wise fashion. The orthogonal functionalization of the ketone/azide copolymers was characterized by NMR and IR spectroscopies and gel-permeation chromatography. A one-pot dual functionalization strategy is also presented that allows for the quantitative dual functionalization of copolymers. This one-pot strategy introduced herein for the preparation of multifunctional macromolecules provides a modular platform for potential applications ranging from electronic materials to polymer-mediated drug delivery.

2.2 Introduction

The synthesis of highly functionalized polymers has been widely investigated since such polymers are potential materials for a variety of applications ranging from electronic devices to biological materials.[1-4] For example, in the context of biological applications, orthogonal multifunctionalization of polymers plays an important role in the fabrication of biomaterials for drug delivery,[2] sensors,[3] and therapeutics.[4] Nature's ability to utilize orthogonal chemistry has been an inspiration for the development of new synthetic functionalization strategies to produce multifunctional polymeric materials. These strategies fall into two main categories, either covalent or noncovalent functionalization.[5] The previous chapter outlined both covalent strategies using click chemistry and noncovalent strategies using supramolecular interactions such as hydrogen bonding and metal coordination. This chapter describes a methodology for the orthogonal functionalizations of random copolymers in quantitative yields under mild reaction conditions *via* covalent functionalization strategies using click reactions: 1,3-dipolar cycloaddition and hydrazone formation.[6,7] The research design follows two important design requirements: (1) a well-controlled polymer scaffold, and (2) distinct and independent functional groups which undergo highly selective and quantitative covalent reactions in an orthogonal fashion (Figure 2.1).

Figure 2.1. Schematic representation of the one-pot covalent multifunctionalization of random copolymers.

The well-defined polymeric scaffold is based on norbornenes as the polymerizable unit. Ring-opening metathesis polymerization (ROMP) was employed using a ruthenium-based initiator.[8] Ruthenium-catalyzed ROMP is highly functional group tolerant, often living, and provides for highly controlled and tailored polymer backbones such as poly(norbornene)s.[9,10] The Weck group has demonstrated that poly(norbornene)-based random as well as block copolymers can be formed using norbornene–precursors with an *exo* stereochemistry.[9d] Furthermore, poly(norbornene)s have been employed as materials in a variety of biological applications. For example, poly(norbornene)s have been utilized as mechanistic probes of receptor clustering in cell signaling by Kiessling and co-workers, who demonstrated that the poly(norbornene)-based multivalent ligands can activate immune responses *in vivo*.[10] In addition, they have employed poly(norbornene)s as polymeric scaffolds to create biologically active multivalent arrays.[11]

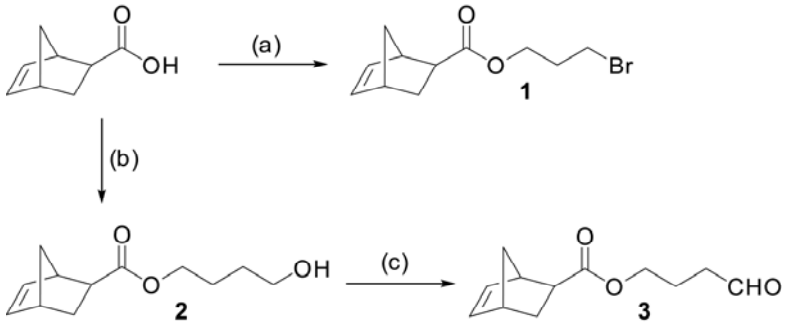
The second requirement was fulfilled by using two different transformations: (i) copper-catalyzed 1,3-dipolar cycloaddition[6] and (ii) hydrazone formation starting with polymer-supported aldehydes and ketones[7]. By appropriate design of these polymers, we present a library of modular functionalizations of the resultant copolymers that involves (a) a single orthogonal functionalization *via* either 1,3-dipolar cycloaddition or hydrazone formation and (b) a one-pot multifunctionalization using both transformations in a single step.

2.3 Results and Discussion

2.3.1 Aldehyde-Based System

Monomers **1** and **3** were prepared starting from isomerically pure *exo*-norbornene acid[12] (Scheme 2.1). *exo*-Norbornene acid was esterified with 3-bromo-1-propanol or 1,4-butanediol using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) to afford **1** and **2**, respectively. Monomer **3** was then synthesized by the oxidation of **2** using pyridinium chlorochromate (PCC).

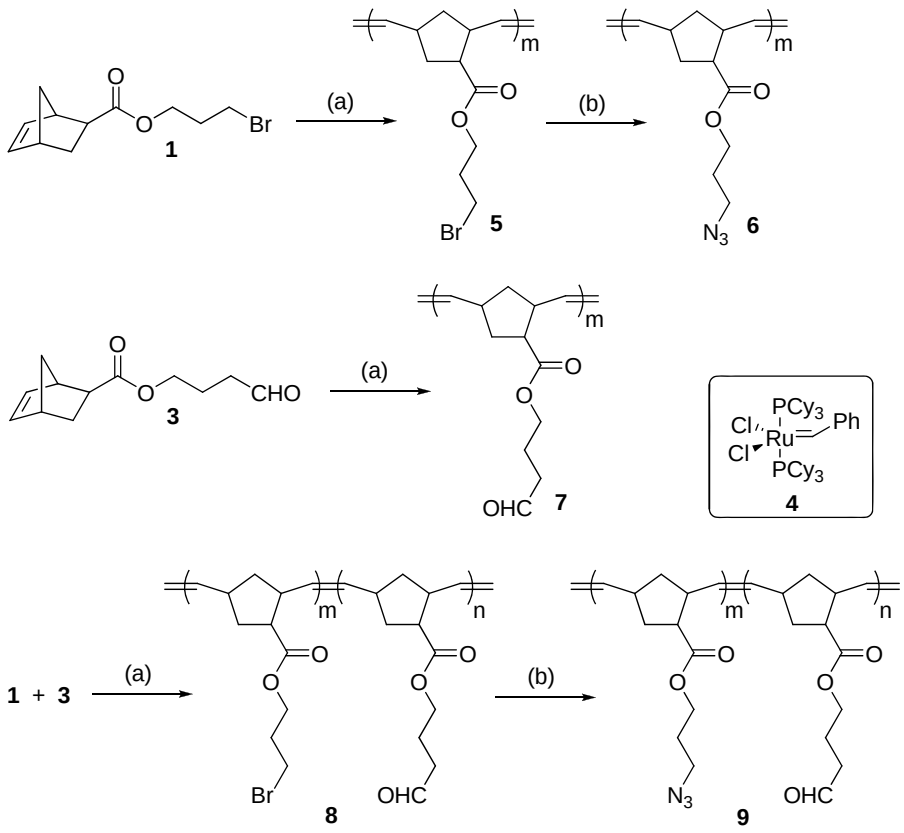
Scheme 2.1. Synthesis of Monomers **1** and **3**.[a]



[a] Reagents and conditions: (a) $Br(CH_2)_3OH$, DCC, DMAP, CH_2Cl_2, 25 °C, 4 h, 96%; (b) $HO(CH_2)_4OH$, DCC, DMAP, CH_2Cl_2, 25 °C, 4 h, 77%; (c) PCC, CH_2Cl_2, 25 °C, 2 h, 80%.

To investigate the polymerization behaviors, monomers **1** and **3** were homopolymerized in dichloromethane using Grubbs' first-generation initiator **4**[13] (Scheme 2.2).

Scheme 2.2. Synthesis of Random Copolymer **9**.[a]



[a] Reagents and conditions: (a) **4**, CH_2Cl_2, 25 °C, 2 h, 97-98%; (b) NaN_3, DMF, 25 °C, 3 h, 96-97%.

In both cases, monomer to initiator ratios ([M]:[I]) of 25:1 were employed and complete conversions were observed within 10 min at room temperature. We also conducted a series of homopolymerizations with [M]:[I] ranging from 25:1 to 125:1 to investigate the control of the polymerization of **1** and **3**. A linear relationship between M_n and [M]:[I] (Figure 2.2) was found for homopolymer **5**, indicating the controlled nature of the polymerization for **1**.

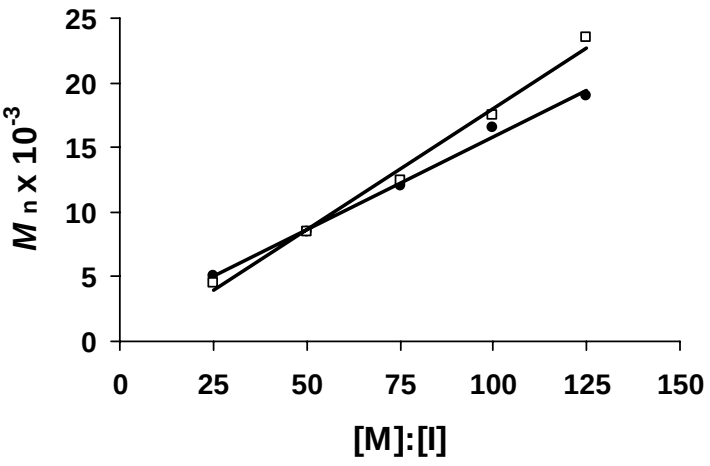


Figure 2.2. Plot of M_n versus monomer/initiator ratios for polymers **5** (●) and **14** (□). Molecular weights are reported versus poly(styrene).

However, the controlled polymerization of **3** could not be fully determined due to the insolubility of the isolated homopolymer **7** in common organic solvents. Nevertheless, full initiations were observed for both homopolymerizations as indicated by complete shifts of the carbene signals of **4** in the ^{1}H NMR spectra from 20.0 ppm before the addition of **1** or **3** to 18.8 ppm after complete initiations. While no signal corresponding to uninitiated **4** was observed, the integration of the former signal at 20.0 ppm and the 'initiated' carbene species at 18.8 ppm were identical suggesting the lack of significant side reactions.

To further characterize the living nature of **1**, we carried out a homoblock copolymerization experiment. First, a 25:1 [M]:[I] ratio of **1**:**4** was polymerized to completion. Subsequently, 375 equivalents of additional **1** were added to the reaction mixture. The gel-permeation chromatography (GPC) trace of the homoblock copolymer after the addition of the 375 equivalents of **1** showed a complete shift to high molecular

weight without traces of terminated low molecular weight polymer (Figure 2.3). This result in conjunction with the linear relationship between M_n and [M]:[I] clearly proves the living nature of the ROMP of **1** using **4**.

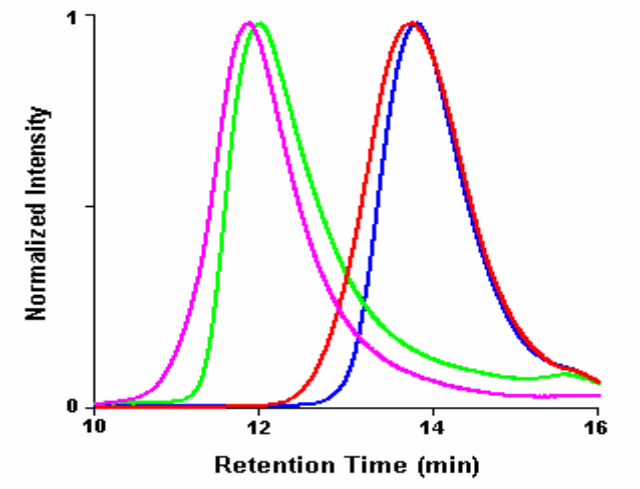


Figure 2.3. GPC traces of the homoblock copolymers prepared using monomers **1** and **13**. Blue trace: polymer **5** after complete conversion ([M]:[I] = 25:1, M_w = 7 500, M_n = 5 000, PDI = 1.54). Green trace: polymer **5** after the addition of 375 equiv of additional monomer **1** ([M]:[I] = 400:1, M_w = 68 000, M_n = 38 500, PDI = 1.78). Red trace: polymer **14** after complete conversion ([M]:[I] = 25:1, M_w = 8 000, M_n = 4 500, PDI = 1.77). Pink trace: polymer **14** after the addition of 375 equiv of additional monomer **13** ([M]:[I] = 400:1, M_w = 101 500, M_n = 55 500, PDI = 1.82). All molecular weights are reported versus poly(styrene).

Initially, the synthesis of a norbornene azide monomer was attempted *via* the azidation of **1**. However, the azide functionality reacted with the highly strained norbornene double bond resulting in inactive monomers. In order to circumvent this problem, a post-polymerization strategy to introduce the azide onto the polymer was developed. Compound **5** was converted to **6** in quantitative yields as confirmed by ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of **6** showed the complete loss of the

bromomethyl resonance at 3.43 ppm and the appearance of a new signal at 3.35 ppm corresponding to the azidomethyl group.

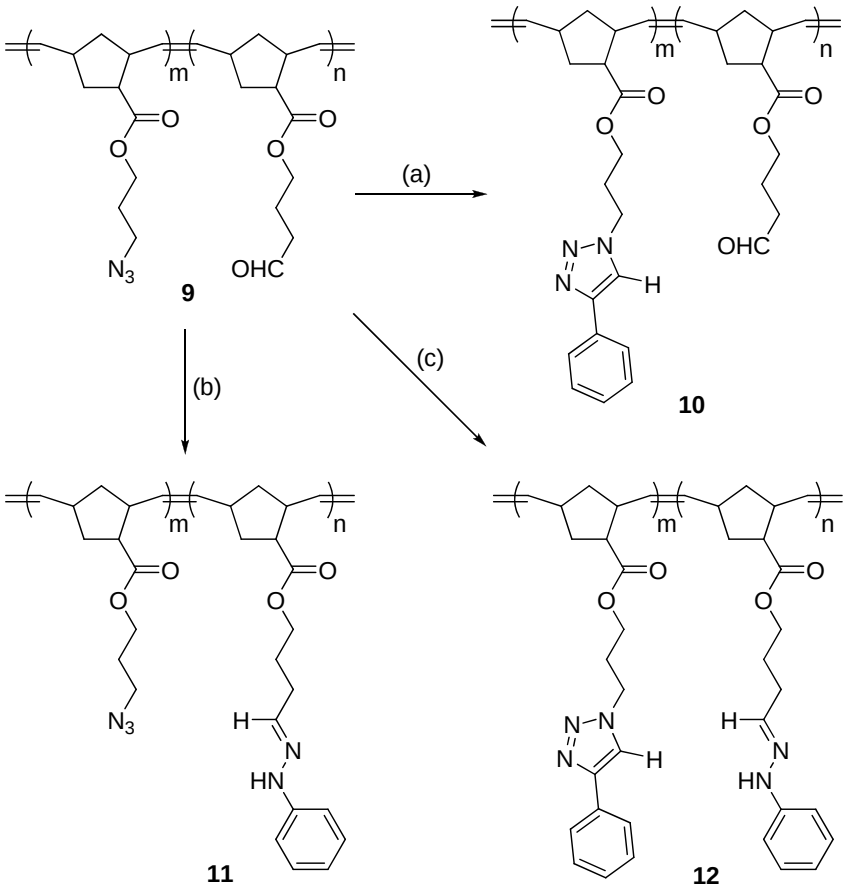
The synthesis of random copolymer **9** was straightforward and is shown in Scheme 2.2. Monomers **1** and **3** were copolymerized quantitatively at 1:1 ratio using 4 mol% of **4**. The Weck group has previously reported that the copolymerization of *exo*-norbornenes proceeds in a random fashion suggesting the formation of random copolymers in the described systems.[9d] Polymer **8** was isolated by precipitation into methanol and reacted with sodium azide to yield target polymer **9** in 96% yield. Unfortunately, isolated **9** was not soluble in common organic solvents. The insolubility of **9** can be attributed to the aldehyde group along the polymer side-chains, which was supported by the insolubility of the aldehyde homopolymer **7**. Aldehydes along polymer backbones have a tendency to take part in inter- and intramolecular hydrogen bonding, dipole-dipole interaction, and/or cross-linking, resulting in insoluble material. A similar phenomenon has been reported recently by Maynard and co-workers,[14] who demonstrated that polymers containing aldehyde side-chains have to be generated *in situ* and used directly without isolation due to the insolubility of the aldehyde polymer.

It was then investigated whether the desired difunctional polymer **9**, which was generated *in situ* without isolation, is able to undergo distinct and independent reactions with functional moieties. To achieve this goal, several requirements must be realized including reactions with near quantitative yields, high fidelities and selectivities, and no interference of the two functional handles, the azide and the aldehyde, with each other during the functionalization steps. 1,3-Dipolar cycloaddition and hydrazone formation fulfill these requirements and were employed in the orthogonal functionalizations of **9**.

Scheme 2.3 shows the orthogonal functionalization strategy of **9**. Functionalization of **9** *via* 1,3-dipolar cycloaddition was accomplished using phenylacetylene as substrate under typical 1,3-dipolar cycloaddition conditions: $CuSO_4 \cdot 5H_2O$ as the catalyst, sodium ascorbate as the ligand, and THF as the solvent. The conversion was confirmed by the ^{1}H NMR spectrum of **10**, which showed the emergence of the triazole proton at 7.82 ppm and a diagnostic downfield shift of the azidomethyl signal from 3.36 ppm to 4.44 ppm. Furthermore, no change of the signal for the aldehyde was observed indicating the stability of the aldehyde groups to the 1,3-dipolar cycloaddition conditions. Copolymer **9** was also treated with phenylhydrazine in THF to obtain **11**. The hydrazone formation was verified by the ^{1}H NMR spectrum of **11**, which showed upfield shifts from 9.78 ppm (-CH_2CHO) to 7.43 ppm (-CH_2CH=N-) and 2.50 ppm (-CH_2CHO) to 2.32 ppm (-CH_2CH=N-). The ^{1}H NMR spectrum also showed that the azide group was unchanged during the hydrazone formation indicating the absence of any unwanted side-reactions. These results demonstrated that (a) both reactions can be carried out on the poly(norbornene) backbone and (b) the two functional handles are orthogonal to each other.

Finally, a one-pot 1,3-dipolar cycloaddition and hydrazone formation of **9** using phenylacetylene and phenylhydrazine was performed. The ^{1}H NMR spectrum of **12** showed the characteristic shifts for both transformations. Unfortunately, after precipitation and isolation, pure polymers **10**, **11**, and **12** were not soluble in common solvents precluding characterization.

Scheme 2.3. Functionalization strategies of **9**.[a]



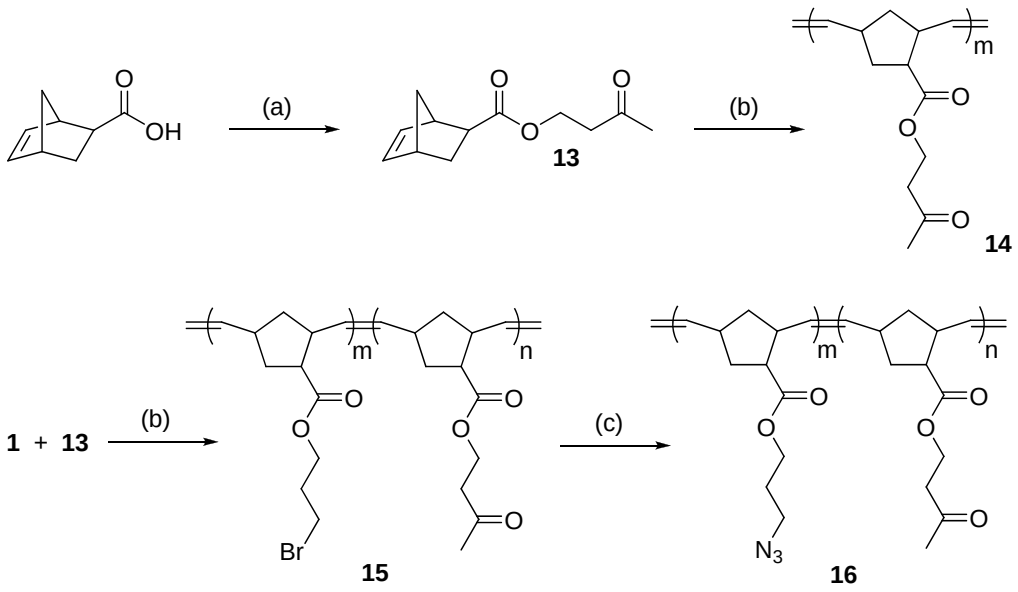
[a] Reagents and conditions: (a) phenylacetylene, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, THF, 65 °C, 5 h; (b) phenylhydrazine, THF, 65 °C, 2 h; (c) phenylacetylene, phenylhydrazine, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, THF, 65 °C, 5 h.

2.3.2 Ketone-Based System

In order to overcome the insolubility of the aldehyde-functionalized polymers, a ketone group was employed for the hydrazone formation instead of the more reactive aldehyde. It is well-known that ketones can also undergo hydrazone formation with hydrazide in high yields.[7] The synthesis of the azide- and ketone-functionalized polymer

16 is outlined in Scheme 2.4. Ketone monomer **13** was synthesized by the DCC-mediated esterification of *exo*-norbornene acid with 4-hydroxy-2-butanone.

Scheme 2.4. Synthesis of Random Copolymer **16**.[a]



[a] Reagents and conditions: (a) 4-hydroxy-2-butanone, DCC, DMAP, CH_2Cl_2, 25 °C, 4 h, 76%; (b) **4**, CH_2Cl_2, 25 °C, 2 h, 98-99%; (c) NaN_3, DMF, 25 °C, 3 h, 96%.

The homopolymerization of monomer **13** was investigated. Complete polymerization of **13** in CH_2Cl_2 with 4 mol% of Grubbs' first-generation initiator **4** was observed. Monomer **13** was also found to polymerize in a living fashion. A linear relationship between M_n and [M]:[I] was established for **13** (Figure 2.2). Furthermore, full initiation was observed by a complete shift of the carbene signal of **4** in the ^1H NMR spectrum from 20.0 ppm to 18.8 ppm after complete initiation. No signal corresponding to the uninitiated ruthenium complex was observed and the integration of the signal before (20.0 pmm) and after the addition of monomer (18.8 ppm) was identical. Finally, a

homoblock copolymerization experiment of **13** was performed. A 25:1 [M]:[I] ratio of **13** was polymerized to completion. Subsequently, 375 equivalents of additional **13** were added. The GPC analysis showed a complete and dramatic shift to high molecular weight without traces of terminated low molecular weight polymer (Figure 2.3). These results in conjunction with the linear relationship between M_n and [M]:[I] clearly prove the living nature of the ROMP of **13**.

With monomers **1** and **13** in hand that both polymerize in a living fashion and therefore allow for full control over molecular weights and degree of polymerization, the copolymerization of **1** and **13** was investigated. The random copolymerization of **1** and **13** at 1:1 ratio using 4 mol% of **4** gave copolymers in 98% isolated yield. Since the kinetics of the homopolymerizations of monomers **1** and **13** are approximately the same within experimental errors (monomer to initiator ratios of 25:1 polymerize in 10 min for both monomers), the copolymerization of **1** and **13** proceeds in a random fashion. The azide-functionalized polymer **16** was synthesized in close analogy to **9** using NaN_3 in DMF in 96% yield. GPC analyses of **15** and **16** were carried out and molecular weights and polydispersity indices (PDIs) were measured (M_n = 12 500, PDI = 1.62 for **15** and M_n = 16 500, PDI = 1.62 for **16**, all versus poly(styrene) standards). The unchanged PDIs indicate that the postpolymerization functionalization step does not change basic polymer properties. Both isolated copolymers **15** and **16** containing ketones along the side-chains were fully soluble in common solvents such as CH_2Cl_2, THF, DMF, and DMSO. Thus, the insolubility problem observed for the aldehyde polymers was overcome by using the ketone-based system.

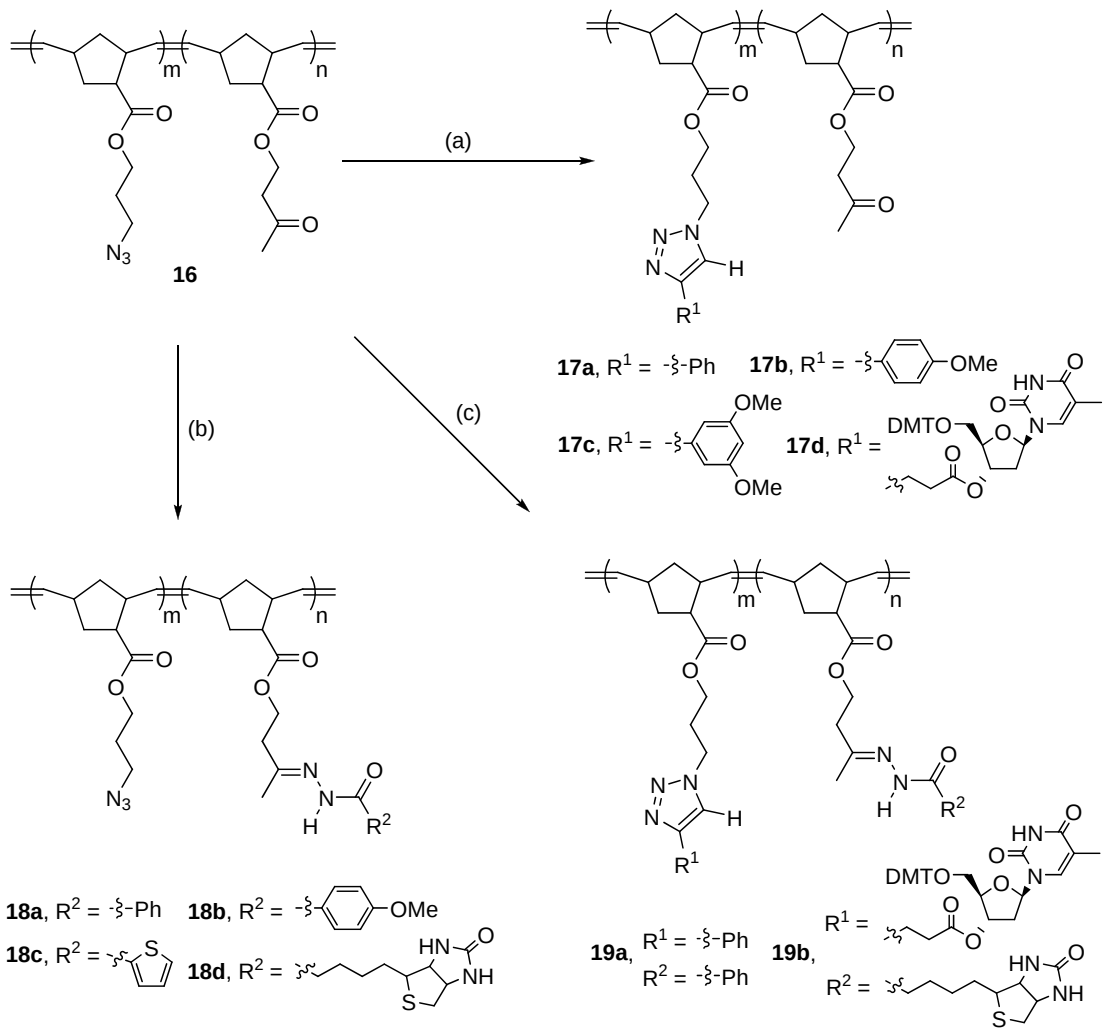
Both, 1,3-dipolar cycloaddition and hydrazone formation, are compatible with a wide range of substrates and reagents allowing for modularity and diversity in the nature of the functional polymer. The modularity and diversity of the orthogonal functionalization strategies of **16** was investigated by reacting a library of compounds with **16** *via* 1,3-dipolar cycloaddition and hydrazone formation as outlined in Scheme 2.5. The one-pot dual functionalization of **16** was also examined.

The 1,3-dipolar cycloaddition transformations were carried out between **16** and phenylacetylene, 4-ethynylanisole, and 4-ethynyl-3,5-dimethoxybenzene under the typical 1,3-dipolar cycloaddition conditions described above (Scheme 2.5, entries 17a-c). In all cases, quantitative conversions of the azide to the corresponding triazole products as indicated by NMR and IR spectroscopies and gel-permeation chromatography were observed. The isolated yields of all azide functionalized copolymers ranged from 97-99%. The ^{1}H NMR spectra of **17a-c** showed the emergence of the triazole protons at 7.73-7.81 ppm and the diagnostic downfield shifts of the azidomethyl signals from 3.35 ppm to 4.42-4.46 ppm, depending upon the acetylene groups. Complete disappearance of azide band of **16** at 2099 cm^{-1} was observed in the IR spectra of **17a-c**. GPC data of **17a-c** revealed M_n ranging from 14 000 to 15 000 and PDIs ranging from 1.82 to 1.88.

To obtain the hydrazone products **18a-c**, **16** was coupled to benzhydrazide, 4-methoxybenzhydrazide, and 2-thiophenecarboxylic acid hydrazide in DMF (Scheme 2.5, entries 18a-c). Quantitative formations in all cases were verified by the characteristic upfield shifts in the ^{1}H NMR spectra from 2.16 ppm [-C(C*H*$_3$)=O] to 1.98-2.04 [-C(C*H*$_3$)=N-] depending upon the hydrazide groups employed and the disappearance of the ketone carbonyl signal at 205.1 ppm in the ^{13}C NMR spectra. Isolated yields of **18a-c**

ranged from 97-99%. GPC data of **18a-c** showed M_n ranging from 10 500 to 13 500 and PDIs ranging from 1.53-2.29.

Scheme 2.5. Functionalization of Copolymer **16**.[a]



[a] Reaction conditions: (a) R^1-CCH, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, THF, 65 °C, 97-99%; (b) R^2-$CONHNH_2$, DMF or DMSO, 25 °C, 97-99%; (c) R^1-CCH, R^2-$CONHNH_2$, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, DMF or DMSO, 25 °C, 96-97%.

One-pot dual functionalization of **16** to **19a** was performed using phenylacetylene and benzhydrazide (Scheme 2.5, entry 19a). Complete conversion to the bifunctionalized product **19a** was observed as characterized by NMR and IR spectroscopies and gel-permeation chromatography. The ^{1}H NMR spectrum of **19a** showed a combination of the characteristic shifts observed for both the **17a** and **18a**. The ^{13}C NMR and IR spectra of **19a** revealed a complete loss of the ketone and azide groups, respectively. The M_n and PDI of **19a** were 10 000 and 1.78, respectively.

As a proof of principle to demonstrate that the functionalization strategy can be employed to yield biological relevant materials and that substrates containing a variety of functionalities that do not interfere with the click chemistry can be utilized, **16** was functionalized with two biologically significant molecules, the alkyne-functionalized nucleoside[15] and the biotin hydrazide. Polymer **16** was quantitatively converted to the nucleoside-functionalized polymer **17d** *via* 1,3-dipolar cycloaddition as characterized by the appearance of the triazole proton at 7.40 ppm and the diagnostic downfield shift of azidomethyl signal from 3.35 to 4.37 ppm in the ^{1}H NMR spectrum as well as complete disappearance of azide band at 2099 cm^{-1} in the IR spectrum. Furthermore, polymer **16** was treated with biotin hydrazide in DMSO to obtain the biotin-functionalized polymer **18d**. The quantitative conversion was confirmed by the characteristic shift in the ^{1}H NMR spectrum from 2.08 ppm [-C(CH_3)=O] to 1.80 [-C(CH_3)=N-] in DMSO-d_6 and the complete loss of the ketone carbonyl signal at 205.1 ppm in the ^{13}C NMR spectra. Finally, the one-pot dual functionalization of **16** was carried out using both alkyne-functionalized nucleoside and biotin hydrazide. Complete conversions to **19b** were verified by a combination of the characteristic shifts observed for **17d** and **18d** as well as the complete

loss of the ketone and azide groups in the ^{13}C NMR and IR spectra of **19b**, respectively. GPC analyses of **17d** and **19b** were carried out (M_n = 17 000, PDI = 1.65 for **17d** and M_n = 15 000, PDI = 1.67 for **19b**. Molecular weights are reported versus poly(styrene) standards). In the case of **18d**, GPC analysis could not be performed because of the insolubility of **18d** in CH_2Cl_2, THF, and DMF.

During all monofunctionalizations of **16** *via* 1,3-dipolar cycloaddition (Scheme 2.5, **17a-d**) or hydrazone formation (Scheme 2.5, **18a-d**), only single products were obtained and no side reactions of any other part or functional group of the polymer or substrates were observed. These results clearly demonstrate that both functionalization methods of **16** are independent of each other and can be addressed in an orthogonal fashion. Furthermore, all functionalizations proceed in quantitative yields and all resulting fully functionalized copolymers were soluble in common solvents demonstrating the synthetic potential of the methodology.

2.4 Conclusion

In this chapter, a novel methodology for the quantitative dual covalent functionalization of copolymers based on highly efficient, versatile, and modular covalent synthetic strategies has been developed. Modular functionalization of the azide- and ketone-functionalized random copolymer was accomplished with small organic and biological molecules containing alkyne or hydrazide groups *via* a single orthogonal functionalization using either 1,3-dipolar cycloaddition or hydrazone formation, and a one-pot multifunctionalization by combining both reactions simultaneously. All investigated functionalization transformations proceed quantitatively in an orthogonal manner with high fidelity and absolute selectivity under mild reaction conditions. Our study demonstrates the potential for the employment of such a single step functionalization strategy in polymeric materials.

2.5. Experimental

All reagents were purchased either from Acros Organics, Alfa Aesar, Sigma-Aldrich, or Strem Chemicals and used without further purification unless otherwise noted. CH_2Cl_2 was dried via passage through copper oxide and alumina columns. NMR spectra were recorded using a Varian Mercury 400 (^{1}H: 400.0 MHz; ^{13}C: 100.6 MHz) or a Varian Mercury 300 (^{1}H: 300.0 MHz; ^{13}C: 75.5 MHz) spectrometer. Chemical shifts are reported in ppm and referenced to the corresponding residual nuclei in deuterated solvents. IR spectra were recorded using a Perkin-Elmer Spectrum 1000 FTIR spectrometer. Elemental analyses were performed using a Perkin-Elmer Series II 2400 CHNS/O analyzer. Mass spectral analyses were provided by the Georgia Tech Mass Spectrometry

Facility using a VG-70se spectrometer. Gel-permeation chromatography (GPC) analyses were carried out using a Shimadzu pump coupled to a Shimadzu UV detector with tetrahydrofuran (THF) as the eluant and a flow rate of 1 mL/min on American Polymer Standards column set (100, 1000, 100 000 Å, linear mixed bed). All GPCs were calibrated using poly(styrene) standards and carried out at room temperature. M_w, M_n, and PDI represent the weight-average molecular weight, number-average molecular weight, and polydispersity index, respectively. *exo*-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid[12] and alkyne-functionalized nucleoside[15] were synthesized according to the previously published procedures.

***exo*-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 3-bromopropyl ester (1).** To a solution of exo-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (1.8 g, 13 mmol) and 3-bromo-1-propanol (2.2 g, 16 mmol) in anhydrous CH_2Cl_2 (20 mL) were added *N*,*N*′-dicyclohexylcarbodiimide (DCC, 3.0 g, 14 mmol) and 4-dimethylaminopyridine (DMAP, catalytic amount). After the mixture was stirred at 25 °C for 4 h, water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a yellow oil that was further purified by column chromatography on silica gel in hexanes/EtOAc (20:1) to yield 3.2 g of a clear oil in 96% yield. ^{1}H NMR ($CDCl_3$): δ 6.13 (m, 2H), 4.23 (t, J = 6.5 Hz, 2H), 3.48 (t, J = 6.5 Hz, 2H), 3.03 (s, 1H), 2.93 (s, 1H), 2.19 (m, 3H), 1.91 (m, 1H), 1.51 (m, 1H), 1.38 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 175.8, 137.9, 135.5, 62.1, 46.7, 46.4, 43.1, 41.7, 31.8, 30.5, 29.6. Anal. Calcd for $C_{11}H_{15}BrO_2$: C, 50.98; H, 5.83. Found: C, 50.97; H, 5.80. EIMS *m*/*z*: calcd for $C_{11}H_{15}BrO_2$, 258.0255; found, 258.0232.

***exo*-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 4-hydroxybutyl ester (2).** To a solution of exo-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (0.70 g, 5.1 mmol) and 1,4-butanediol (1.4 g, 15 mmol) in anhydrous CH_2Cl_2 (15 mL) were added DCC (1.2 g, 5.6 mmol) and DMAP (catalytic amount). After the mixture was stirred at 25 °C for 4 h, water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a yellow oil that was further purified by column chromatography on silica gel in hexanes/EtOAc (3:1) to yield 0.82 g of a clear oil in 77% yield. ^{1}H NMR ($CDCl_3$): δ6.10 (m, 2H), 4.11 (t, J = 6.5 Hz, 2H), 3.65 (t, J = 6.5 Hz, 2H), 3.01 (s, 1H), 2.90 (s, 1H), 2.20 (m, 1H), 1.89 (m, 1H), 1.71 (m, 2H), 1.63 (m, 2H), 1.49 (m, 1H), 1.34 (m, 2H). ^{13}C NMR ($CDCl_3$): δ176.1, 137.8, 135.5, 64.2, 62.3, 46.6, 46.4, 43.2, 41.7, 30.4, 29.2, 25.2. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.48; H, 8.76. EIMS *m*/*z*: calcd for $C_{12}H_{18}O_3$, 210.1256; found, 210.1241.

***exo*-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 4-oxobutyl ester (3).** Compound **2** (0.19 g, 0.90 mmol) and pyridinium chlorochromate (PCC, 0.29 g, 1.4 mmol) were dissolved in CH_2Cl_2 (10 mL) and stirred at 25 °C for 2 h. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a yellow oil that was further purified by column chromatography on silica gel in hexanes/EtOAc (3:1) to yield 0.15 g of a clear oil in 77% yield. ^{1}H NMR ($CDCl_3$): δ9.77 (s, 1H), 6.10 (m, 2H), 4.09 (t, J = 7.0 Hz, 2H), 2.99 (s, 1H), 2.89 (s, 1H), 2.53 (t, J =7.0 Hz, 2H), 2.18 (m, 1H), 1.96 (m, 2H), 1.86 (m, 1H), 1.46 (m, 1H), 1.34 (m, 2H). ^{13}C NMR ($CDCl_3$): δ200.9, 175.8, 137.8, 135.4, 63.3, 46.5, 46.3, 43.1, 41.6, 40.5, 30.3, 21.5. Anal.

Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.95; H, 8.02. EIMS *m*/*z*: calcd for $C_{12}H_{16}O_3$, 208.1099; found, 208.1085.

Polymer 5. Monomer **1** (0.12 g, 0.47 mmol) was dissolved in anhydrous, degassed CH_2Cl_2 (1 mL) under an argon atmosphere. Ruthenium initiator **4** (15 mg, 0.019 mmol) was added as a solution in CH_2Cl_2 (0.5 mL). Upon complete polymerization, ethyl vinyl ether was added to quench the polymerization. Polymer **5** was isolated by repeated precipitations into cold MeOH (0.12 g, 97%). ^{1}H NMR ($CDCl_3$): δ 5.48-5.16 (br, 2H), 4.19 (br, 2H), 3.43 (br, 2H), 3.16-2.88 (br, 1H), 2.78-2.47 (br, 2H), 2.15 (br, 2H), 2.07 (br, 1H), 1.95 (br, 1H), 1.67 (br, 1H), 1.18 (br, 1H). ^{13}C NMR ($CDCl_3$): δ 175.4, 134.3, 133.4, 132.3, 131.0, 62.0, 49.4, 47.8, 41.9, 41.2, 36.2, 31.8, 29.6. GPC: M_w = 7.5 kDa, M_n = 5.0 kDa, and PDI = 1.54.

Polymer 6. To a solution of polymer **5** (0.11 g, 0.42 mmol) in anhydrous DMF (2 mL) was added NaN_3 (82 mg, 1.3 mmol). After the mixture was stirred at 25 °C for 3 h, water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water and concentrated under reduced pressure to give a dark brown oil that was further purified by precipitations into cold MeOH (91 mg, 97%). ^{1}H NMR ($CDCl_3$): δ 5.50-5.16 (br, 2H), 4.13 (br, 2H), 3.35(br, 2H), 3.16-2.86 (br, 1H), 2.78-2.46 (br, 2H), 2.13-1.82 (br, 4H), 1.67 (br, 1H), 1.20 (br, 1H). ^{13}C NMR ($CDCl_3$): δ 175.6, 133.5, 132.5, 132.0, 131.1, 61.1, 49.3, 48.1, 47.6, 41.8, 41.0, 36.1, 28.1. GPC: M_w = 12.0 kDa, M_n = 6.5 kDa, and PDI = 1.88.

Polymer 7. Monomer **3** (0.12 g, 0.56 mmol) was dissolved in anhydrous, degassed CH_2Cl_2 (1 mL) under an argon atmosphere. Ruthenium initiator **4** (18 mg, 0.022 mmol) was added as a solution in CH_2Cl_2 (0.5 mL). Upon complete polymerization, ethyl vinyl

ether was added to quench the polymerization. Polymer **7** was isolated by repeated precipitations into cold MeOH (0.12 g, 98%). ^{1}H NMR ($CDCl_3$): δ 9.78 (s, 1H), 5.46-5.16 (br, 2H), 4.09 (br, 2H), 3.16-2.89 (br, 1H), 2.77-2.44 (br, 4H), 2.09-1.78 (br, 4H), 1.67 (br, 1H), 1.20 (br, 1H).

Polymer 8. Monomers **1** (0.38 g, 1.5 mmol) and **3** (0.31 g, 1.5 mmol) were dissolved in anhydrous, degassed CH_2Cl_2 (10 mL) under an argon atmosphere. Ruthenium initiator **4** (49 mg, 0.059 mmol) was added as a solution in CH_2Cl_2 (1 mL). Upon complete polymerization, ethyl vinyl ether was added to quench the polymerization. Polymer **8** was isolated by repeated precipitations into cold MeOH (0.68 g, 98%). ^{1}H NMR ($CDCl_3$): δ 9.78 (s, 1H), 5.46-5.17 (br, 4H), 4.20 (br, 2H), 4.09 (br, 2H), 3.44 (br, 2H), 3.14-2.87 (br, 2H), 2.77-2.45 (br, 6H), 2.21-1.87 (br, 8H), 1.64 (br, 2H), 1.17 (br, 2H). ^{13}C NMR ($CDCl_3$): δ 201.1, 175.6, 133.5, 132.5, 132.1, 131.1, 63.3, 62.0, 50.1, 49.4, 47.8, 41.9, 41.1, 40.5, 36.2, 31.7, 29.7, 29.5, 27.0, 26.8, 26.3, 26.1, 21.4.

Polymer 9. Polymer **8** (0.65 g, 1.4 mmol) generated *in situ* and NaN_3 (0.27 mg, 4.2 mmol) were dissolved in anhydrous DMF (10 mL) and stirred at 25 °C for 3 h. Water (150 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water and concentrated under reduced pressure to give a dark brown oil that was further purified by precipitations into cold MeOH (0.57 g, 96%). ^{1}H NMR ($CDCl_3$): δ 9.77 (s, 1H), 5.46-5.16 (br, 4H), 4.18-4.05 (br, 4H), 3.36 (br, 2H), 3.16-2.83 (br, 2H), 2.76-2.44 (br, 6H), 2.10-1.86 (br, 8H), 1.67 (br, 2H), 1.20 (br, 2H). ^{13}C NMR ($CDCl_3$): δ 201.2, 175.6, 133.6, 132.5, 132.1, 131.2, 63.3, 61.2, 50.1, 49.4, 48.2, 47.6, 43.1, 41.9, 41.1, 40.5, 37.2, 36.8, 36.5, 36.1, 28.2, 21.4.

Polymer 10. To a solution of polymer **9** (0.10 g, 0.23 mmol) generated *in situ* and phenylacetylene (36 mg, 0.35 mmol) in THF (5 mL) were added $CuSO_4 \cdot 5H_2O$ (2.8 mg, 0.011 mmol) and sodium ascorbate (4.4 mg, 0.022 mmol). After the mixture was stirred at 65 °C for 5 h, water was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water and concentrated under reduced pressure. The residue was precipitated into cold MeOH to afford polymer **10**. ^{1}H NMR ($CDCl_3$): δ 9.78 (s, 1H), 7.82 (br, 3H), 7.40 (br, 2H), 7.33 (br, 1H), 5.44-5.15 (br, 4H), 4.44 (br, 2H), 4.25-4.00 (br, 4H), 3.16-2.86 (br, 2H), 2.78-2.44 (br, 6H), 2.26 (br, 2H), 2.10-1.84 (br, 6H), 1.64 (br, 2H), 1.18 (br, 2H).

Polymer 11. Polymer **9** (0.10 g, 0.23 mmol) generated *in situ* and phenylhydrazine (38 mg, 0.35 mmol) were dissolved in THF (5 mL). The mixture was stirred at 65 °C for 2 h and then concentrated under reduced pressure. The residue was precipitated into cold MeOH to afford polymer **11**. ^{1}H NMR ($CDCl_3$): δ 7.43 (br, 1H), 7.22 (br, 2H), 7.04 (br, 1H), 6.98 (br, 1H), 6.82 (br, 2H), 5.44-5.12 (br, 4H), 4.25-4.05 (br, 4H), 3.36 (br, 2H), 3.16-2.83 (br, 2H), 2.80-2.42 (br, 4H), 2.32 (br, 2H), 2.08-1.78 (br, 8H), 1.64 (br, 2H), 1.18 (br, 2H).

Polymer 12. To a solution of polymer **9** (0.10 g, 0.23 mmol) generated *in situ*, phenylacetylene (36 mg, 0.35 mmol), and phenylhydrazine (38 mg, 0.35 mmol) in THF (5 mL) were added $CuSO_4 \cdot 5H_2O$ (2.8 mg, 0.011 mmol) and sodium ascorbate (4.4 mg, 0.022 mmol). After the mixture was stirred at 65 °C for 5 h, water was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water and concentrated under reduced pressure. The residue was precipitated into cold MeOH to afford polymer **12**. ^{1}H NMR ($CDCl_3$): δ 7.82 (br, 3H),

7.58-6.78 (br, 10H), 5.43-5.12 (br, 4H), 4.44 (br, 2H), 4.20-4.02 (br, 4H), 3.16-2.83 (br, 2H), 2.82-2.42 (br, 4H), 2.40-2.16 (br, 4H), 2.10-1.08 (br, 10H).

***exo*-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 3-oxobutyl ester (13).** To a solution of *exo*-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (1.0 g, 7.2 mmol) and 4-hydroxy-2-butanone (77 mg, 8.7 mmol) in anhydrous CH_2Cl_2 (15 mL) were added DCC (1.6 g, 8.0 mmol) and DMAP (catalytic amount). After the mixture was stirred at 25 °C for 12 h, water (20 mL) was added and then the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a yellow oil that was further purified by column chromatography on silica gel in hexanes/EtOAc (4:1) to yield 1.3 g of a clear oil in 72% yield. ^{1}H NMR ($CDCl_3$): δ 6.10 (m, 2H), 4.33 (t, J = 6.4 Hz, 2H), 2.98 (s, 1H), 2.89 (s, 1H), 2.76 (t, J = 6.4 Hz, 2H), 2.18 (s, 3H), 2.17 (m, 1H), 1.87 (m, 1H), 1.47 (m, 1H), 1.34 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 205.4, 175.8, 137.9, 135.5, 59.3, 46.6, 46.3, 43.0, 42.4, 41.6, 30.4, 30.3. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.93; H, 7.54. EIMS *m*/*z*: calcd for $C_{12}H_{16}O_3$, 208.1099; found, 208.1072.

Polymer 14. Monomer **13** (0.10 mg, 0.48 mmol) was dissolved in anhydrous, degassed CH_2Cl_2 (1 mL) under an argon atmosphere. Ruthenium initiator **4** (16 mg, 0.019 mmol) was added as a solution in CH_2Cl_2 (0.5 mL). Upon complete polymerization, ethyl vinyl ether was added to quench the polymerization. Polymer **14** was isolated by repeated precipitations into cold MeOH (0.10 g, 99%). ^{1}H NMR ($CDCl_3$): δ 5.49-5.15 (br, 2H), 4.31 (br, 2H), 3.20-2.45 (br, 5H), 2.18 (s, 3H), 2.12-1.89 (br, 2H), 1.66 (br, 1H), 1.19 (br, 1H). ^{13}C NMR ($CDCl_3$): δ 205.5, 175.6, 133.4, 132.5, 132.0, 131.0, 59.2, 49.2, 47.3, 42.3, 41.8, 40.9, 36.1, 30.2. GPC: M_w = 8.0 kDa, M_n = 4.5 kDa, and PDI = 1.77.

Polymer 15. Monomers **1** (0.71 g, 2.7 mmol) and **13** (0.57 mg, 2.7 mmol) were dissolved in anhydrous, degassed CH_2Cl_2 (20 mL) under an argon atmosphere. Ruthenium initiator **4** (90 mg, 0.11 mmol) was added as a solution in CH_2Cl_2 (2 mL). Upon complete polymerization, ethyl vinyl ether was added to quench the polymerization. Polymer **15** was isolated by repeated precipitations into cold MeOH (1.2 g, 98 %). ^{1}H NMR ($CDCl_3$): δ 5.43-5.13 (br, 4H), 4.29 (br, 2H), 4.18 (br, 2H), 3.42 (br, 2H), 3.14-2.86 (br, 2H), 2.78-2.42 (br, 6H), 2.19-1.86 (br, 9H), 1.63 (br, 2H), 1.16 (br, 2H). ^{13}C NMR ($CDCl_3$): δ 205.2, 175.3, 133.3, 132.3, 131.9, 130.9, 62.0, 59.2, 50.2, 49.3, 47.8, 47.4, 42.4, 41.9, 41.2, 41.0, 37.2, 36.8, 36.2, 31.7, 30.3, 29.6. IR (KBr): 2955, 2854, 1728, 1445, 1389, 1361, 1256, 1164, 1045, 969, 757 cm^{-1}. GPC: M_w = 20.0 kDa, M_n = 12.5 kDa, and PDI = 1.62.

Polymer 16. To a solution of polymer **15** (1.1 g, 2.3 mmol) in anhydrous DMF (15 mL) was added NaN_3 (0.44 g, 6.8 mmol). After the mixture was stirred at 25 °C for 3 h, water (200 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with water and concentrated under reduced pressure to give a dark brown oil that was further purified by precipitations into cold MeOH (0.94 g, 96 %). ^{1}H NMR ($CDCl_3$): δ 5.44-5.14 (br, 4H), 4.29 (br, 2H), 4.13 (br, 2H), 3.35 (br, 2H), 3.14-2.86 (br, 2H), 2.77-2.43 (br, 6H), 2.16 (s, 3H), 2.07-1.83 (br, 6H), 1.63 (br, 2H), 1.16 (br, 2H). ^{13}C NMR ($CDCl_3$): δ 205.2, 175.4, 133.3, 132.3, 131.9, 131.0, 61.2, 59.2, 50.1, 49.3, 48.1, 47.7, 47.4, 42.4, 41.8, 41.0, 37.2, 36.8, 36.2, 36.1, 30.3, 28.3. IR (KBr): 2947, 2846, 2099, 1733, 1717, 1699, 1456, 1393, 1360, 1259, 1165, 1044, 969, 751 cm^{-1}. GPC: M_w = 27.0 kDa, M_n = 16.5 kDa, and PDI = 1.62.

General Procedure for the 1,3-Dipolar Cycloaddition. To a solution of polymer **16** and alkyne in THF were added $CuSO_4 \cdot 5H_2O$ (5 mol%) and sodium ascorbate (10 mol%).

After the mixture was stirred at 65 °C for 5 h, water was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with water and concentrated under reduced pressure. The residue was purified by precipitations into cold MeOH to afford the polymers **17a-d**.

Polymer 17a. Polymer **17a** (97 mg, 99%) was obtained from **16** (79 mg, 0.18 mmol) and phenylacetylene (21 mg, 0.21 mmol). ^{1}H NMR ($CDCl_3$): δ 7.81 (br, 3H), 7.40 (br, 2H), 7.32 (br, 1H), 5.47-5.13 (br, 4H), 4.46 (br, 2H), 4.30 (br, 2H), 4.13 (br, 2H), 3.16-2.84 (br, 2H), 2.79-2.43 (br, 6H), 2.27 (br, 2H), 2.16 (s, 3H), 2.09-1.83 (br, 4H), 1.65 (br, 2H), 1.17 (br, 2H). ^{13}C NMR ($CDCl_3$): δ 205.3, 175.3, 147.5, 133.4, 132.3, 132.0, 130.9, 130.3, 128.7, 128.0, 125.5, 119.9, 60.8, 59.2, 50.1, 49.3, 47.6, 47.2, 42.3, 41.8, 41.1, 40.8, 37.3, 36.8, 36.2, 30.3, 29.7, 29.6. IR (KBr): 3136, 2957, 2856, 1733, 1717, 1699, 1611, 1485, 1455, 1436, 1360, 1260, 1164, 1078, 1043, 972, 804, 767, 696 cm^{-1}. GPC: M_w = 27.5 kDa, M_n = 15.0 kDa, and PDI = 1.85.

Polymer 17b. Polymer **17b** (70 mg, 98%) was obtained from **16** (55 mg, 0.13 mmol) and 4-ethynylanisole (17 mg, 0.13 mmol). ^{1}H NMR ($CDCl_3$): δ 7.73 (br, 3H), 6.93 (br, 2H), 5.48-5.12 (br, 4H), 4.44 (br, 2H), 4.29 (br, 2H), 4.12 (br, 2H), 3.82 (s, 3H), 3.14-2.40 (br, 8H), 2.25 (br, 2H), 2.16 (s, 3H), 2.09-1.82 (br, 4H), 1.65 (br, 2H), 1.16 (br, 2H). ^{13}C NMR ($CDCl_3$): δ 205.3, 175.4, 159.3, 147.4, 133.3, 132.4, 132.0, 131.0, 126.8, 123.1, 119.0, 114.1, 60.8, 59.2, 55.3, 50.1, 49.3, 47.7, 47.2, 42.4, 41.9, 41.7, 41.1, 37.4, 36.9, 36.2, 30.3, 29.8, 29.7. IR (KBr): 3138, 2959, 2858, 1733, 1717, 1699, 1616, 1558, 1501, 1456, 1418, 1360, 1250, 1175, 1031, 973, 837, 798, 668 cm^{-1}. GPC: M_w = 29.5 kDa, M_n = 16.0 kDa, and PDI = 1.82.

Polymer 17c. Polymer **17c** (53 mg, 97%) was obtained from **16** (40 mg, 0.093 mmol) and 4-ethynyl-3,5-dimethoxybenzene (15 mg, 0.093 mmol). ^{1}H NMR ($CDCl_3$): δ 7.81 (br, 1H), 6.98 (br, 2H), 6.43 (br, 1H), 5.47-5.13 (br, 4H), 4.46 (br, 2H), 4.30 (br, 2H), 4.12 (br, 2H), 3.82 (s, 6H), 3.14-2.41 (br, 8H), 2.26 (br, 2H), 2.16 (s, 3H), 2.08-1.83 (br, 4H), 1.64 (br, 2H), 1.15 (br, 2H). ^{13}C NMR ($CDCl_3$): δ 205.3, 175.3, 160.9, 147.5, 133.4, 132.4, 132.1, 132.0, 131.0, 120.1, 103.6, 100.3, 60.8, 59.2, 55.5, 50.1, 49.4, 47.8, 47.3, 42.4, 41.9, 41.7, 41.0, 37.2, 36.8, 36.2, 30.3, 29.7. IR (KBr): 3125, 2947, 2846, 1728, 1717, 1699, 1598, 1557, 1456, 1422, 1362, 1278, 1204, 1156, 1064, 1042, 969, 926, 831, 688 cm^{-1}. GPC: M_w = 26.5 kDa, M_n = 14.0 kDa, and PDI = 1.88.

Polymer 17d. Polymer **17d** (0.12 g, 99%) was obtained from **16** (50 mg, 0.12 mmol) and alkyne-functionalized nucleoside (73 mg, 0.12 mmol). ^{1}H NMR ($CDCl_3$): δ 10.10-9.36 (br, 1H), 7.60 (s, 1H), 7.51-7.20 (br, 10H), 6.82 (br, 4H), 6.38 (br, 1H), 5.52-5.16 (br, 5H), 4.37 (br, 2H), 4.30 (br, 2H), 4.15-4.01 (br, 3H), 3.77 (s, 6H), 3.45 (br, 2H), 3.13-2.33 (br, 14H), 2.24-1.85 (br, 9H), 1.66 (br, 2H), 1.35 (s, 3H), 1.18 (br, 2H). ^{13}C NMR ($CDCl_3$): δ 205.4, 175.3, 171.8, 163.9, 158.5, 150.4, 145.6, 143.9, 135.2, 135.0, 134.9, 133.3, 132.3, 132.1, 131.0, 129.9, 127.9, 127.8, 127.0, 121.1, 113.2, 111.5, 87.1, 84.2, 83.8, 75.6, 63.7, 60.8, 59.2, 55.3, 50.0, 49.3, 47.5, 46.9, 42.4, 41.9, 41.0, 37.9, 37.2, 36.9, 36.2, 33.6, 30.3, 29.7, 29.6, 20.9, 11.7. IR (KBr): 3140, 3040, 2951, 2830, 2252, 1738, 1733, 1717, 1699, 1695, 1683, 1674, 1668, 1652, 1635, 1608, 1583, 1557, 1511, 1464, 1456 1447, 1362, 1252, 1176, 1106, 1076, 1033, 968, 913, 829, 792, 755, 729, 703, 647 cm^{-1}. GPC: M_w = 28.0 kDa, M_n = 17.0 kDa, and PDI = 1.65.

General Procedure for Hydrazone Formation. Polymer **16** and the hydrazide of interest were dissolved in anhydrous, degassed DMF (for **18a-c**) or DMSO (for **18d**). The

mixture was stirred at 25 °C for 2 h (for **18a-c**) or 24 h (for **18d**) and then concentrated *in vacuo*. The residue was precipitated into cold hexanes or MeOH and then washed with MeOH to afford the polymers **18a-d**.

Polymer 18a. Polymer **18a** (50 mg, 99%) was obtained from **16** (40 mg, 0.093 mmol) and benzhydrazide (13 mg, 0.093 mmol).^{1}H NMR ($CDCl_3$): δ 9.82-8.68 (br, 1H), 7.77 (br, 2H), 7.40 (br, 3H), 5.43-5.11 (br, 4H), 4.40-4.02 (br, 4H), 3.34 (br, 2H), 3.13-2.39 (br, 8H), 2.14-1.78 (br, 9H), 1.62 (br, 2H), 1.14 (br, 2H). ^{13}C NMR ($CDCl_3$): δ 175.4, 163.9, 155.4, 137.1, 133.2, 132.2, 131.7, 131.0, 130.1, 128.5, 127.1, 61.2, 50.1, 49.3, 48.1, 47.6, 47.3, 43.1, 41.8, 41.0, 38.3, 37.2, 36.9, 36.1, 30.4, 28.2, 16.2. IR (KBr): 3210, 2951, 2850, 2098, 1733, 1717, 1699, 1668, 1652, 1634, 1520, 1489, 1456, 1393, 1362, 1262, 1170, 1029, 969, 914, 801, 696 cm^{-1}. GPC: M_w = 24.5 kDa, M_n = 13.5 kDa, and PDI = 1.84.

Polymer 18b. Polymer **18b** (91 mg, 97%) was obtained from **16** (70 mg, 0.16 mmol) and 4-methoxybenzhydrazide (27 mg, 0.16 mmol).^{1}H NMR ($CDCl_3$) δ 9.73-8.72 (br, 1H), 7.79 (br, 2H), 6.89 (br, 2H), 5.45-5.13 (br, 4H), 4.38-4.05 (br, 4H), 3.82 (s, 3H), 3.34 (br, 2H), 3.12-2.33 (br, 8H), 2.14-1.80 (br, 9H), 1.63 (br, 2H), 1.15 (br, 2H). ^{13}C NMR ($CDCl_3$): δ 175.4, 162.2, 154.8, 137.2, 134.1, 133.2, 132.3, 131.0, 129.0, 125.3, 113.7, 61.2, 55.4, 50.1, 49.3, 48.1, 47.6, 47.2, 43.1, 42.4, 41.8, 41.0, 38.3, 37.2, 36.8, 36.2, 28.2, 15.8. IR (KBr): 3210, 2960, 2859, 2098, 1733, 1717, 1699, 1652, 1606, 1538, 1505, 1456, 1360, 1257, 1176, 1029, 969, 914, 844, 801, 763, 668 cm^{-1}. GPC: M_w = 16.0 kDa, M_n = 10.5 kDa, and PDI = 1.53.

Polymer 18c. Polymer **18c** (46 mg, 98%) was obtained from **16** (36 mg, 0.084 mmol) and 2-thiophenecarboxylic acid hydrazide (12 mg, 0.084 mmol). ^{1}H NMR ($CDCl_3$): δ 10.51-9.50 (br, 1H), 8.12 (br, 1H), 7.61 (br, 1H), 7.10 (br, 1H), 5.48-5.09 (br, 4H),

4.55-4.07 (br, 4H), 3.36 (br, 2H), 3.16-2.39 (br, 8H), 2.16-1.81 (br, 9H), 1.64 (br, 2H), 1.15 (br, 2H). ^{13}C NMR ($CDCl_3$): δ 175.4, 163.1, 150.0, 135.1, 134.5, 133.3, 132.9, 132.3, 131.0, 128.3, 126.2, 61.2, 50.1, 49.3, 48.2, 47.7, 47.2, 43.1, 42.6, 41.9, 41.1, 37.9, 37.2, 36.8, 36.2, 28.3, 16.0. IR (KBr): 3190, 2950, 2849, 2098, 1733, 1717, 1699, 1651, 1634, 1622, 1516, 1456, 1418, 1394, 1256, 1170, 1035, 968, 914, 844, 720 cm^{-1}. GPC: M_w = 30.5 kDa, M_n = 13.5 kDa, and PDI = 2.29.

Polymer 18d. Polymer **18d** (48 mg, 98%) was obtained from **16** (32 mg, 0.074 mmol) and biotin hydrazide (19 mg, 0.074 mmol). ^{1}H NMR (DMSO-d_6): δ 10.30-9.89 (br, 1H), 6.42 (s, 1H), 6.35 (s, 1H), 5.49-5.11 (br, 4H), 4.32-3.98 (br, 6H), 3.36 (br, 2H), 3.12-2.76 (br, 5H), 2.67-2.15 (br, 8H), 2.03-1.73 (br, 9H), 1.67-1.40 (br, 6H), 1.31 (br, 2H), 1.14 (br, 2H). ^{13}C NMR (DMSO-d_6): δ 174.9, 168.6, 162.7, 137.7, 134.0, 133.4, 132.4, 131.4, 61.0, 59.2, 55.4, 48.7, 47.6, 47.2, 46.8, 41.6, 41.3, 37.2, 36.8, 35.9, 35.5, 33.6, 33.2, 32.0, 28.3, 28.1, 28.0, 27.7, 25.2, 24.1, 16.4, 10.8. IR (KBr): 3261, 2940, 2863, 2099, 1732, 1703, 1699, 1694, 1683, 1674, 1652, 1538, 1455, 1435, 1393, 1333, 1264, 1170, 1026, 968, 824, 762, 686 cm^{-1}. GPC analysis was not performed because of the insolubility of **18d** in CH_2Cl_2, THF, and DMF.

General Procedure for One-pot 1,3-Dipolar Cycloaddition and Hydrazone Formation. To a solution of polymer **16**, alkyne, and hydrazide in anhydrous, degassed DMF (for **19a**) or DMSO (for **19b**) were added $CuSO_4 \cdot 5H_2O$ (5 mol%) and sodium ascorbate (10 mol%). The mixture was stirred at 25 °C for 24 h and then concentrated *in vacuo*. The residue was precipitated into cold hexanes or MeOH and then washed with MeOH to afford the polymers **19a-b**.

Polymer 19a. Polymer **19a** (66 mg, 97%) was obtained from **16** (45 mg, 0.10 mmol), phenylacetylene (11 mg, 0.10 mmol), and benzhydrazide (14 mg, 0.10 mmol). ^{1}H NMR ($CDCl_3$): δ 9.41-8.68 (br, 1H), 7.79 (br, 5H), 7.59-7.25 (br, 6H), 5.50-5.07 (br, 4H), 4.56-4.01 (br, 6H), 3.14-2.41 (br, 8H), 2.24 (br, 2H), 2.14-1.80 (br, 7H), 1.63 (br, 2H), 1.15 (br, 2H). ^{13}C NMR ($CDCl_3$): δ 175.6, 169.7, 147.7, 133.7, 133.4, 132.4, 132.2, 131.8, 131.6, 131.1, 130.4, 128.8, 128.6, 128.1, 125.6, 119.9, 61.1, 60.8, 49.2, 47.6, 47.4, 47.2, 42.3, 41.8, 41.7, 40.9, 37.2, 36.8, 36.2, 36.0, 29.4. IR (KBr): 3190, 2951, 2850, 1729, 1717, 1675, 1525, 1486, 1451, 1370, 1260, 1170, 1077, 1027, 971, 763, 696 cm^{-1}. GPC: M_w = 18.0 kDa, M_n = 10.0 kDa, and PDI = 1.78.

Polymer 19b. Polymer **19b** (72 mg, 96%) was obtained from **16** (25 mg, 0.058 mmol), alkyne-functionalized nucleoside (36 mg, 0.058 mmol), and biotin hydrazide (15 mg, 0.058 mmol). ^{1}H NMR (DMSO-d_6): δ 11.88, 10.02 (br, 1H), 11.37 (s, 1H), 7.81 (s, 1H), 7.49 (s, 1H), 7.39-7.11 (br, 9H), 6.91-6.77 (br, 4H), 6.42 (s, 1H), 6.36 (s, 1H), 6.18 (br, 1H), 5.58-5.06 (br, 5H), 4.40-3.82 (br, 9H), 3.68 (s, 6H), 3.28-2.14 (br, 21H), 2.02 (br, 2H), 1.97-1.64 (br, 7H), 1.63-0.97 (br, 13H). ^{13}C NMR (DMSO-d_6): δ 174.8, 171.7, 171.0, 163.6, 162.8, 158.2, 150.4, 144.5, 135.5, 135.3, 135.1, 134.0, 133.4, 132.4, 131.4, 129.7, 128.0, 127.6, 126.9, 121.9, 113.3, 110.0, 86.1, 83.7, 82.9, 74.6, 63.7, 61.0, 60.9, 59.2, 55.4, 55.0, 48.9, 47.5, 46.2, 42.5, 42.0, 41.6, 37.4, 36.3, 33.4, 32.9, 32.7, 28.9, 28.4, 28.2, 28.1, 26.0, 25.3, 24.5, 24.2, 20.5, 13.7, 11.6. IR (KBr): 3262, 3040, 2936, 2830, 1738, 1728, 1703, 1699, 1694, 1683, 1674, 1668, 1652, 1608, 1509, 1464, 1447, 1370, 1252, 1177, 1107, 1029, 969, 914, 829, 791, 757, 727, 703 cm^{-1}. GPC: M_w = 25.0 kDa, M_n = 15.0 kDa, and PDI = 1.67.

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CHAPTER 3

FUNCTIONALIZATION OF RANDOM TERPOLYMERS THROUGH CLICK REACTIONS

3.1 Abstract

Random poly(norbornene)-based terpolymers containing azide, ketone and maleimide functionalities along the side-chain were synthesized using ring-opening metathesis polymerization. Subsequent side-chain functionalizations were carried out using three distinct reactions: maleimide-thiol coupling, 1,3-dipolar cycloaddition, and hydrazone formation. All investigated functionalization transformations proceed with high fidelity and absolute selectivity under mild reaction conditions.

3.2 Introduction

The synthesis of highly functionalized terpolymers is desirable for a variety of applications ranging from electronic devices to biological materials.[1] For example, terpolymers have been investigated as drug delivery vehicles since they can contain targeting moieties such as peptides, antibodies, or sugars and solubilizing groups in addition to the target drug.[2] One strategy to create polymer-drug conjugates is *via* post-polymerization functionalization of polymer side-chains which does not change basic polymer properties such as the degree of polymerization and polydispersities within a series.[3] This approach has yielded stable polymer-drug conjugates which can be delivered to a target site without any unwanted loss.

In the previous chapter, a two monomer-based copolymer system that could be functionalized in quantitative yields in an orthogonal fashion under mild reaction conditions *via* a combination of 1,3-dipolar cycloaddition and hydrazone formation was discussed.[4] A requirement for the successful covalent functionalization of terpolymers is the selection of three different transformations that can proceed indepedently between their corresponding functionalities (Figure 3.1). The coupling of thiols onto maleimides which is a key reaction for the attachment of peptides onto polymers also fulfills the click reaction criteria described in Chapter 1 and can be employed in addition to the two previous transformations.[5] Herein, a methodology for the quantitative functionalization of terpolymers *via* covalent strategies using click chemistry is presented. The combination of the three different transformations allows for fast and precise site-specific functionalization with a limited number of purification steps.

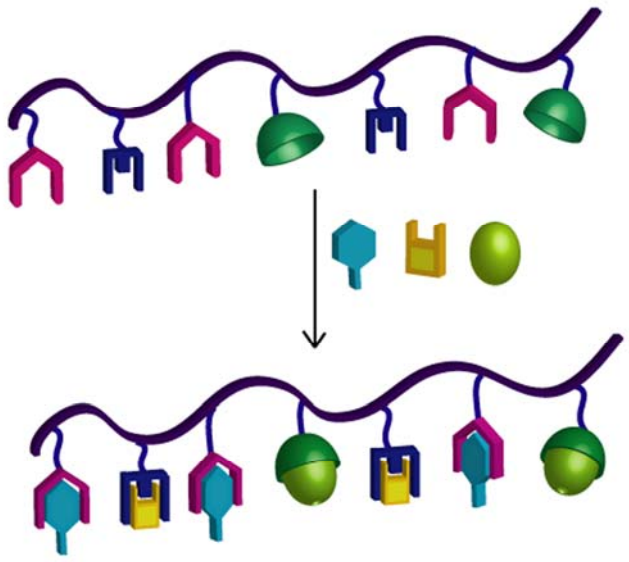
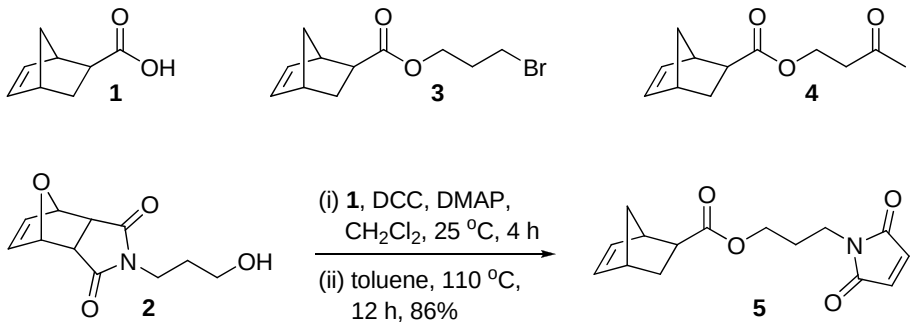


Figure 3.1. Schematic representation of the covalent and orthogonal multi-functionalization of terpolymers.

3.3 Results and Discussion

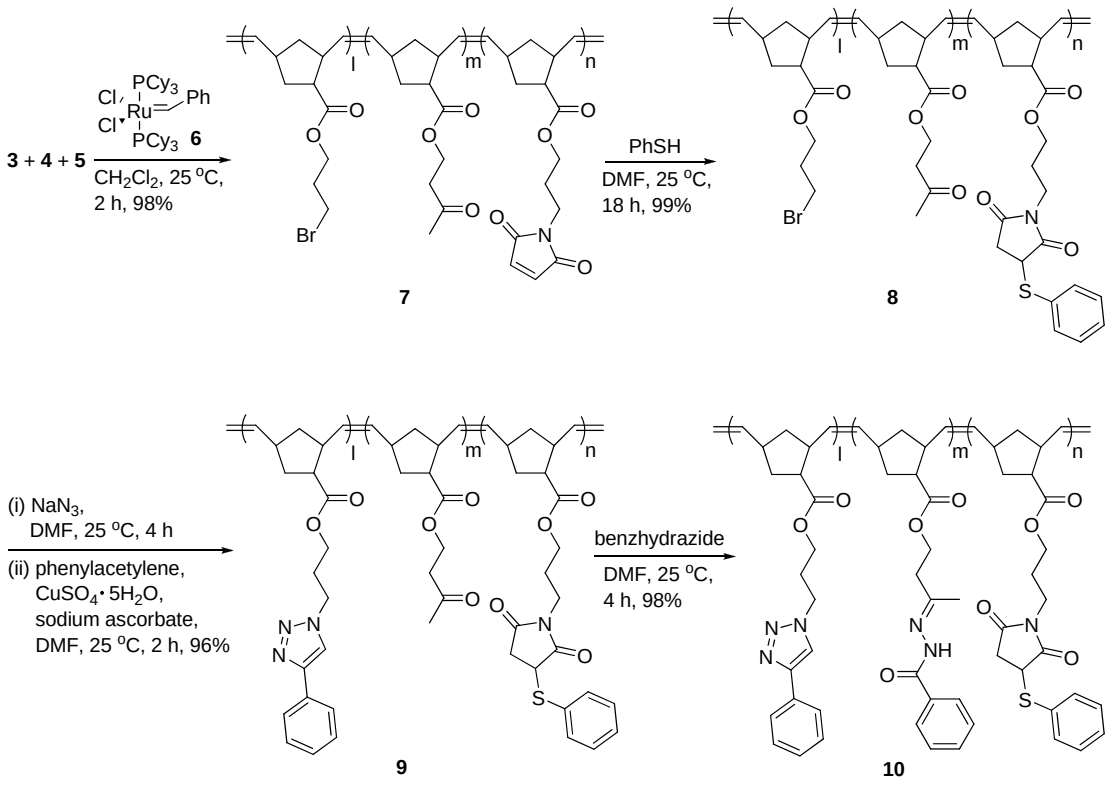
The terpolymer is based on norbornenes **3**-**5** bearing functional groups suitable for subsequent covalent functionalization (Scheme 3.1). The synthesis and homopolymerization behavior by ring-opening metathesis polymerization (ROMP)[6] of the monomers **3** and **4** were reported in the previous chapter.[4] Maleimide monomer **5** was synthesized by the *N*,*N*'-dicyclohexylcarbodiimide-mediated esterification of *exo*-norbornene acid **1** with **2** followed by deprotection using retro-Diels-Alder reaction. To investigate whether the polymerization of **5** is controlled, a series of homopolymerizations using monomer **5** and Grubbs' first-generation initiator **6**[7] with monomer to catalyst ratios ([M]:[I]) ranging from 25:1 to 125:1 was conducted. While 25:1 and 50:1 [M]:[I] ratios of **5**:**6** were polymerized to completion, ratios of 75:1 to 125:1 were not completely polymerized, suggesting an uncontrolled nature of the ROMP of **5**.

Scheme 3.1. Monomers **1**-**4** and synthesis of monomer **5**.



The synthesis and stepwise functionalization strategy of random terpolymer **7** is outlined in Scheme 3.2. Monomers **3**, **4**, and **5** were copolymerized quantitatively using 4 mol % of **6** to obtain **7**.

Scheme 3.2. Synthesis and covalent multi-functionalization of terpolymer **7**. Monomers **3**, **4**, and **5** were polymerized in a random fashion (l:m:n: ratio is 25:25:25).



With random terpolymer **7** in hand, the orthogonal and stepwise functionalization strategies of **7** *via* maleimide-thiol coupling, 1,3-dipolar cycloaddition, and hydrazone formation was investigated. First, **7** was coupled to benzenethiol in DMF to obtain the monofunctional terpolymer **8**. The quantitative conversion was confirmed by the ^{1}H NMR spectrum of **8**, which showed the complete loss of the maleimide double bond resonance at 6.70 ppm (a) and the appearance of the resulting succinimide methine signal

at 4.03 ppm (a') (Figure 3.2.B). Subsequently, **8** was reacted with sodium azide in DMF, followed by 1,3-dipolar cycloaddition of azides generated *in situ* without isolation with phenylacetylene under typical 1,3-dipolar cycloaddition conditions using $CuSO_4 \cdot 5H_2O$ and sodium ascorbate to obtain the bifunctional terpolymer **9**. The quantitative azide formation was verified by a characteristic upfield shift in the ^{1}H NMR spectrum from 3.43 ppm (b, -C*H*$_2$Br) to 3.36 ppm (b', -C*H*$_2$N$_3$) (Figure 3.2.C). Quantitative conversion of the azide to the corresponding triazole product **9** was observed as indicated by the ^{1}H NMR spectrum of **9**, which showed the emergence of the triazole proton at 7.81 ppm (c) and a diagnostic downfield shift of the azidomethyl signal from 3.36 ppm (b') to 4.47 ppm (b'') (Figure 3.2.D). Finally, **9** was coupled to benzhydrazide in DMF to obtain the fully loaded functional terpolymer **10**. The quantitative hydrazone formation was confirmed by a characteristic upfield shift in the ^{1}H NMR spectrum from 2.16 ppm [d, -C(C*H*$_3$)=O] to 1.96 ppm [d', -C(C*H*$_3$)=N-] (Figure 3.2.E) and the disappearance of the ketone carbonyl signal at 205.5 ppm in the ^{13}C NMR spectrum. The combined NMR spectroscopic studies reveal that the stepwise terpolymer functionalization is achieved without affecting the terpolymer backbone and other functional groups. These results demonstrate that the three covalent functionalization steps act independently of each other and can be applied to random terpolymers in an orthogonal and stepwise fashion. Furthermore, all functionalizations proceed in quantitative yields (isolated yields of **8**-**10** are in excess of 96%) and all resulting functionalized terpolymers are fully soluble in common organic solvents such as CH_2Cl_2, THF, DMF, and DMSO, demonstrating the synthetic potential of our methodology.

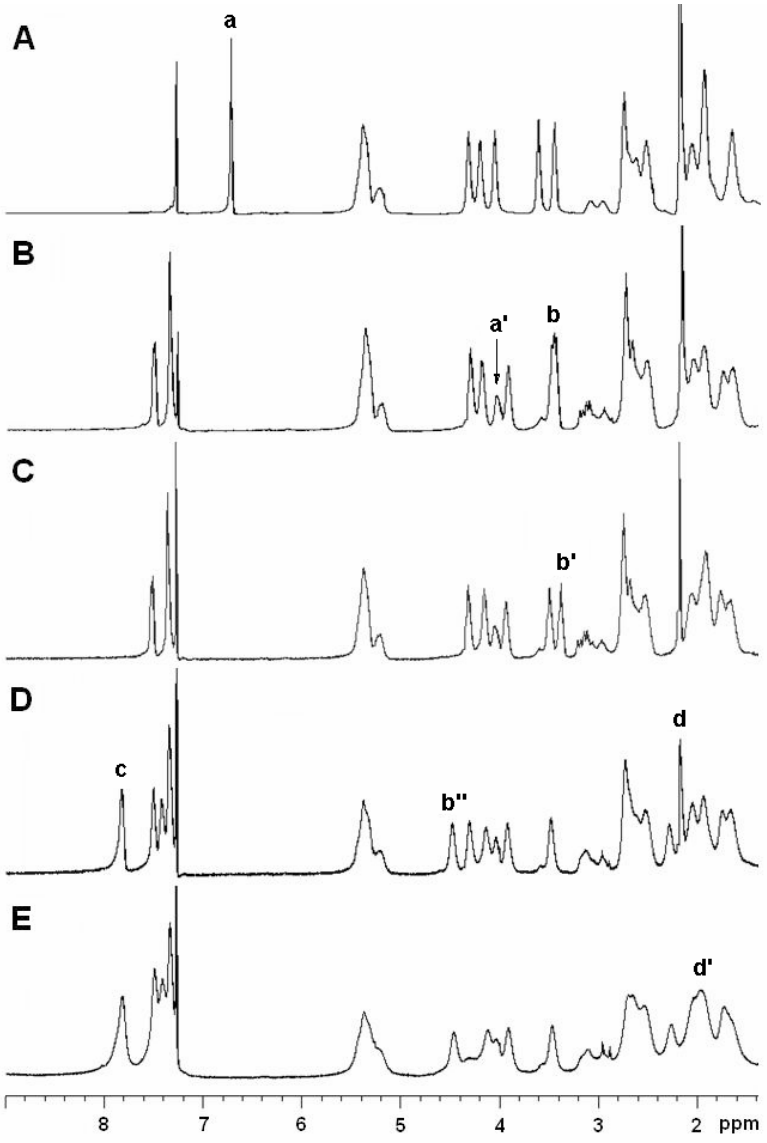


Figure 3.2. Partial ^{1}H NMR spectra in $CDCl_3$ showing the stepwise functionalization of terpolymer **7**: (A) terpolymer **7**; (B) monofunctional terpolymer **8**; (C) azide-functionalized terpolymer from **8**; (D) bifunctional terpolymer **9**; (E) fully trifunctionalized terpolymer **10**.

3.4 Conclusion

This chapter introduced a unique methodology for the quantitative multifunctionalization of random terpolymers based on highly efficient and versatile covalent synthetic strategies using click reactions: maleimide-thiol coupling, 1,3-dipolar cycloaddition, and hydrazone formation. ^{1}H NMR spectroscopic studies have proven that all investigated functionalization transformations proceed quantitatively with high fidelity and absolute selectivity under mild reaction conditions. Therefore, this covalent functionalization strategy will be useful for creating materials for various applications in drug delivery, biosensors, therapeutics, nanotechnology, and combinatorial chemistry.

3.5 Experimental

All reagents were purchased either from Acros Organics, Alfa Aesar, Sigma-Aldrich, or Strem Chemicals and used without further purification unless otherwise noted. CH_2Cl_2 was dried via passage through copper oxide and alumina columns. NMR spectra were recorded using a Varian Mercury 400 (^{1}H: 400.0 MHz; ^{13}C: 100.6 MHz) or a Varian Mercury 300 (^{1}H: 300.0 MHz; ^{13}C: 75.5 MHz) spectrometer. Chemical shifts are reported in ppm and referenced to the corresponding residual nuclei in deuterated solvents. Elemental analyses were performed using a Carlo Erba 1108 elemental analyzer. Gel-permeation chromatography (GPC) analyses were carried out using an Agilent 1200 series isocratic pump coupled to an Agilent UV detector and a Wyatt refractive index detector with dichloromethane as the eluant and a flow rate of 1 mL/min on American Polymer Standards column set (AM GPC gel Linear 10 um and AM GPC gel 500A 10u). All GPCs were calibrated using poly(styrene) standards and carried out at room

temperature. M_w, M_n, and PDI represent the weight-average molecular weight, number-average molecular weight, and polydispersity index, respectively. *exo*-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid **1**,[8] **2**,[9] and monomers **3** and **4**[4] were synthesized according to the previously published procedures.

Monomer 5. To a solution of *exo*-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid **1** (1.5 g, 11 mmol) and compound **2** (2.8 g, 13 mmol) in anhydrous CH_2Cl_2 (20 mL) were added *N*,*N*′-dicyclohexylcarbodiimide (DCC, 2.4 g, 12 mmol) and 4-dimethylaminopyridine (DMAP, catalytic amount). After the mixture was stirred at 25 °C for 4 h, the solvent was removed under reduced pressure. The residue was redissolved in toluene (30 mL), stirred at reflux for 12 h, cooled to room temperature, and concentrated *in vacuo*. Water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a yellow oil that was further purified by column chromatography on silica gel in Hexanes/EtOAc (4:1) to yield 2.5 g of a yellow solid in 86% yield. ^{1}H NMR ($CDCl_3$): δ 6.70 (s, 2H), 6.12 (m, 2H), 4.07 (t, J = 6.0 Hz, 2H), 3.64 (t, J = 6.8 Hz, 2H), 3.06 (s, 1H), 2.92 (s, 1H), 2.21 (m, 1H), 1.96 (m, 3H), 1.53 (m, 1H), 1.36 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 175.9, 170.4, 137.9, 135.6, 134.0, 61.6, 46.6, 46.4, 43.1, 41.7, 35.0, 30.4, 27.7. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.65; H, 6.30; N, 5.07.

Polymer 7. Monomers **3** (0.12 g, 0.47 mmol), **4** (0.10 g, 0.47 mmol), and **5** (0.13 g, 0.47 mmol) were dissolved in anhydrous, degassed CH_2Cl_2 (10 mL) under an argon atmosphere. Ruthenium initiator **6** (16 mg, 0.019 mmol) was added as a solution in CH_2Cl_2 (1 mL). Upon complete polymerization, ethyl vinyl ether was added to quench

the polymerization. Polymer **7** was isolated by repeated precipitations into cold MeOH (0.34 g, 98%). ^{1}H NMR ($CDCl_3$): δ 6.70 (s, 2H), 5.48-5.12 (br, 6H), 4.31 (br, 2H), 4.20 (br, 2H), 4.04 (br, 2H), 3.60 (br, 2H), 3.44 (br, 2H), 3.16-2.84 (br, 3H), 2.82-2.42 (br, 9H), 2.26-1.82 (br, 12H), 1.65 (br, 3H), 1.17 (br, 3H). ^{13}C NMR ($CDCl_3$): δ 205.5, 175.7, 175.6, 170.6, 134.2, 133.5, 132.6, 132.1, 131.8, 131.2, 62.0, 61.5, 59.3, 50.1, 49.6, 49.4, 47.8, 47.4, 42.9, 42.4, 41.9, 41.0, 37.2, 36.9, 36.2, 34.9, 31.8, 30.3, 29.5, 27.7, 27.0, 26.9, 26.4, 26.3, 26.2. GPC: M_w = 41.0 kDa, M_n = 22.0 kDa, and PDI = 1.84.

Polymer 8. To a solution of polymer **7** (85 mg, 0.11 mmol) in anhydrous DMF (2 mL) was added benzenethiol (25 mg, 0.22 mmol). The mixture was stirred at 25 °C for 18 h and then concentrated *in vacuo*. The residue was precipitated into cold MeOH and then washed with MeOH to afford polymer **8** (97 mg, 99%). ^{1}H NMR ($CDCl_3$): δ 7.49 (br, 2H), 7.34 (br, 3H), 5.48-5.12 (br, 6H), 4.30 (br, 2H), 4.17 (br, 2H), 4.03 (br, 1H), 3.91 (br, 2H), 3.44 (br, 4H), 3.21-2.82 (br, 5H), 2.80-2.36 (br, 9H), 2.20-1.46 (br, 15H), 1.16 (br, 3H). ^{13}C NMR ($CDCl_3$): δ 205.5, 175.6, 175.3, 174.3, 134.5, 133.5, 132.5, 132.1, 131.1, 130.2, 129.4, 129.0, 128.5, 127.4, 127.1, 125.9, 61.9, 61.3, 59.2, 50.0, 49.3, 47.7, 47.4, 43.9, 42.3, 41.8, 40.9, 37.1, 36.8, 36.1, 36.0, 31.7, 30.2, 29.5, 26.7. GPC: M_w = 34.0 kDa, M_n = 17.0 kDa, and PDI = 2.06.

Polymer 9. To a solution of polymer **8** (53 mg, 0.062 mmol) in anhydrous DMF (2 mL) was added NaN_3 (4.5 mg, 0.069 mmol). After the mixture was stirred at 25 °C for 4 h, phenylacetylene (13 mg, 0.13 mmol), $CuSO_4 \cdot 5H_2O$ (5 mol%), and sodium ascorbate (10 mol%) were added. Following stirring at 25 °C for 2 h, the mixture was concentrated *in vacuo* and redissolved in CH_2Cl_2. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with

water and concentrated under reduced pressure. The residue was purified by precipitations into cold MeOH to afford polymer **9** (55 mg, 96%). ^{1}H NMR ($CDCl_3$): δ 7.81 (br, 3H), 7.49 (br, 2H), 7.41 (br, 2H), 7.33 (br, 4H), 5.52-5.12 (br, 6H), 4.47 (br, 2H), 4.29 (br, 2H), 4.12 (br, 2H), 4.03 (br, 1H), 3.91 (br, 2H), 3.46 (br, 2H), 3.21-2.84 (br, 5H), 2.78-2.38 (br, 9H), 2.27 (br, 2H), 2.20-1.46 (br, 13H), 1.16 (br, 3H). ^{13}C NMR ($CDCl_3$): δ 205.5, 175.6, 175.3, 174.3, 147.8, 134.5, 133.5, 132.5, 132.1, 131.2, 130.5, 130.2, 129.4, 128.9, 128.2, 125.7, 120.0, 61.3, 60.8, 59.2, 50.1, 49.3, 47.6, 47.4, 47.2, 43.9, 42.3, 41.9, 41.0, 37.2, 36.8, 36.1, 30.3, 29.7, 29.6, 26.8. GPC: M_w = 45.0 kDa, M_n = 20.0 kDa, and PDI = 2.25.

Polymer 10. Benzhydrazide (4.5 mg, 0.033 mmol) was added to a solution of **9** (15 mg, 0.016 mmol) in anhydrous DMF (2 mL). The mixture was stirred at 25 °C for 4 h and then concentrated *in vacuo*. The residue was precipitated into cold MeOH and washed with MeOH to afford polymer **10** (16 mg, 98%). ^{1}H NMR ($CDCl_3$): δ 9.35-8.65 (br, 1H), 7.80 (br, 5H), 7.60-7.12 (br, 11H), 5.48-5.12 (br, 6H), 4.52-3.83 (br, 9H), 3.45 (br, 2H), 3.24-1.46 (br, 29H), 1.16 (br, 3H). ^{13}C NMR ($CDCl_3$): δ 175.4, 174.1, 134.3, 133.4, 132.4, 131.1, 130.3, 129.2, 128.7, 128.1, 125.5, 120.0, 61.3, 60.8, 49.3, 47.2, 44.0, 41.9, 40.9, 36.2, 29.8, 29.6, 26.9. GPC: M_w = 87.0 kDa, M_n = 30.0 kDa, and PDI = 2.92.

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CHAPTER 4

SUPRAMOLECULAR MULTIBLOCK COPOLYMERS

4.1 Abstract

A bimetallic ruthenium olefin metathesis initiator was synthesized and used to polymerize functionalized norbornenes, affording polymers that are living at both polymer chain-ends. Using this bis-ruthenium initiator strategy and combining it with functional chain-terminators, highly efficient syntheses of either SCS-Pd(II) pincer- or pyridine-functionalized symmetrical telechelic polymers were developed. The terminal functional group incorporation was confirmed by ^{1}H NMR spectroscopy analyses. The telechelic polymers were self-assembled into block copolymers *via* metal coordination between corresponding terminal recognition units. The self-assembly process was monitored by ^{1}H NMR spectroscopy revealing nearly quantitative functionalization. The resulting supramolecular block copolymers were further characterized by viscometry and dynamic light scattering.

4.2 Introduction

The introduction of noncovalent interactions between polymeric constituents[1] allows for the modular construction of well-defined supramolecular polymeric assemblies including supramolecular block copolymers, which are of considerable interest due to their promise for applications ranging from electronics to medicine.[2-4] Multiblock copolymers are of particular interest since unprecedented polymeric blends with tunable physical properties can be obtained easily by mixing two appropriately functionalized

homopolymers.[4,5] A number of noncovalent interactions have been used as key interactions in multiblock copolymers including hydrogen bonding and metal coordination, as described in chapter 1.

Ring-opening metathesis polymerization (ROMP) of cyclic olefins in the presence of bifunctional chain-transfer agents (CTA) is an efficient strategy for the incorporation of supramolecular functionalities onto both chain-ends of a polymer.[6] While highly advantageous over traditional post-polymerization functionalization due to complete incorporation of almost any terminal recognition unit *in situ*, the ROMP-CTA strategy limits full control over the obtained telechelic polymer properties since it relies on the non-living polymerization of functionalized cyclooctenes.[5] This chapter reports the synthesis of symmetrically end-functionalized polymers in a single step *via* ROMP using a bimetallic ruthenium initiator and functional chain-terminators (CTs). The combination of a living/controlled polymerization with metal coordination-based self-assembly allows for the formation of well-defined supramolecular alternating block copolymers (Figure 4.1).

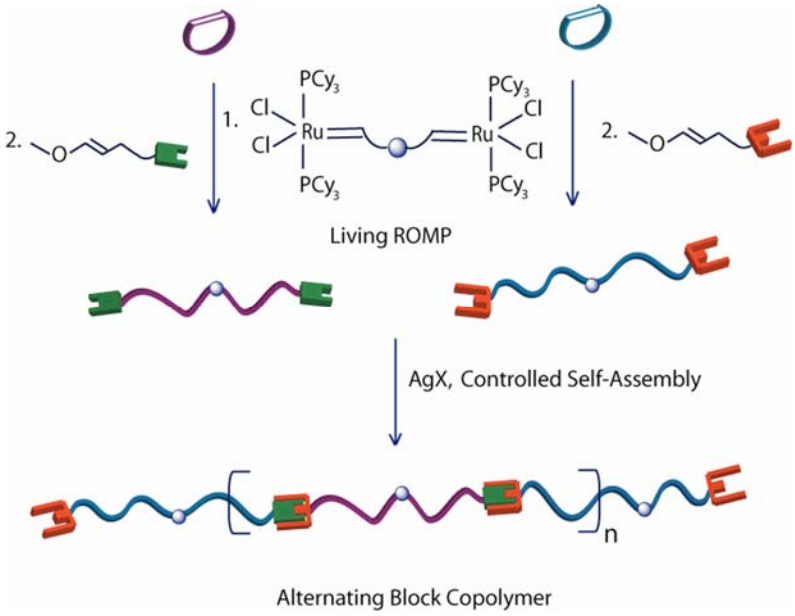


Figure 4.1. Schematic representation of the synthetic strategy towards supramolecular alternating block copolymers.

4.3 Research Design

The strategy is based on the self-assembly of A-A and B-B bifunctional macromonomers *via* metal coordination. The macromonomers are telechelic polymers bearing palladated sulfur-carbon-sulfur (SCS) pincer complex or pyridyl end groups, respectively, at both chain-ends. The telechelic polymers are being synthesized by ROMP using a bis-ruthenium initiator designed to be living and tolerant to a broad range of functionalities,[7] terminated with functional CTs containing metal coordination sites resulting in the formation of perfect telechelic polymers. For this study, the coordination of Pd-pincer complexes to functionalized pyridines was employed as the noncovalent interaction. This metal coordination step is unsymmetrical, highly directional and avoids the problem of homodimerization unlike hydrogen-bonded systems.[8] The combination of

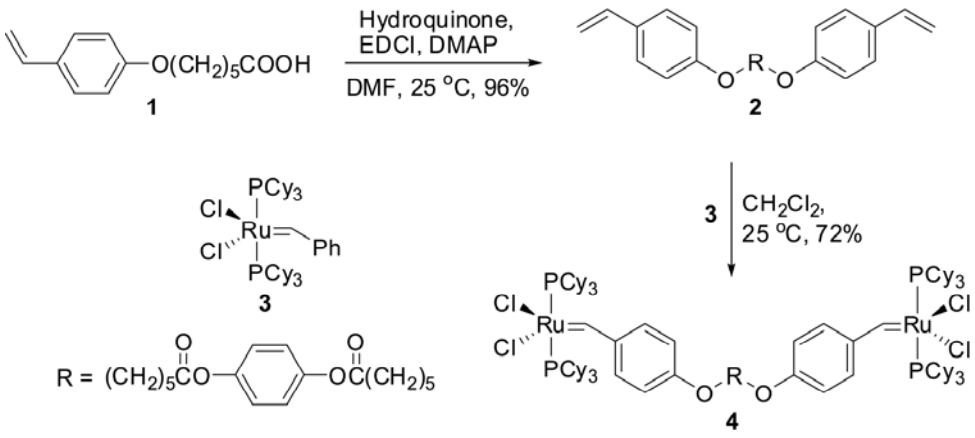
a bis-ruthenium initiator with functionalized CTs is designed to afford symmetrical telechelic polymers possessing desired recognition motifs with full control over basic polymer properties such as molecular weight, degree of polymerization, and polydispersity. Metal coordination between SCS-Pd(II) pincer complex-containing polymers and ones containing pyridyl end groups should lead to the self-assembly of A-A and B-B macromonomers with tunable block length by the controlled addition of the activating agent $AgBF_4$. Furthermore, use of differently substituted norbornene monomers for the A-A and B-B macromonomers allows for the preparation of supramolecular alternating block copolymers.

4.4 Results and Discussion

4.4.1 Bis-Ruthenium Initiator Synthesis

A bis-alkylidene ruthenium olefin metathesis initiator was used to afford poly(norbornene)s that are living at both polymer chain-ends, thereby allowing for complete incorporation of terminal recognition units. The synthesis of the bimetallic ruthenium initiator **4** is outlined in Scheme 4.1. 6-(4-Vinylphenoxy) hexanoic acid **1** was esterified with hydroquinone using *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride and 4-dimethylaminopyridine to afford bis-styrene **2**. Initiator **4** was synthesized by the carbene exchange of **3** with **2** in dichloromethane. ^{1}H NMR analysis indicated 95% conversion to **4** as seen by a shift of the carbene signals to 19.4 ppm in CD_2Cl_2. After purification by column chromatography, **4** was isolated in 72% yield.

Scheme 4.1. Synthesis of bis-ruthenium initiator **4**.



4.4.2 Homopolymerization Using Bis-Ruthenium Initiator

First, the polymerization behaviour of norbornene octyl ester **10** was investigated. Monomer **10** was polymerized quantitatively using 2.5 mol% of **4** within 10 min at room temperature. Full initiation was observed by a complete shift of the carbene signal from 19.4 ppm for **4** to 18.6 ppm (for the fully initiated species) in the ^{1}H NMR spectrum. Then, a series of homopolymerizations with monomer-to-initiator ratios ([M]/[I]) ranging from 40:1 to 200:1 was carried out. A linear relationship between M_n and [M]/[I] was found for polymers **12a-e** (Figure 4.2) indicating the controlled nature of the polymerization of **10** using **4**. The gel-permeation chromatography (GPC) data of **12a-e** are summarized in Table 4.1. The living nature of the polymerization was further confirmed by the synthesis of a homoblock copolymer. First, a 40 mer was synthesized using **4** which was then used as a macroinitiator for the polymerization of a 1000 mer. The GPC traces of the homoblock copolymers were unimodal. Furthermore, a complete shift to high molecular weights without traces of terminated low molecular weight

polymer was observed (Figure 4.3). The new bis-ruthenium initiator **4** is thus not only active toward ROMP of norbornenes but also living at both chain-ends.

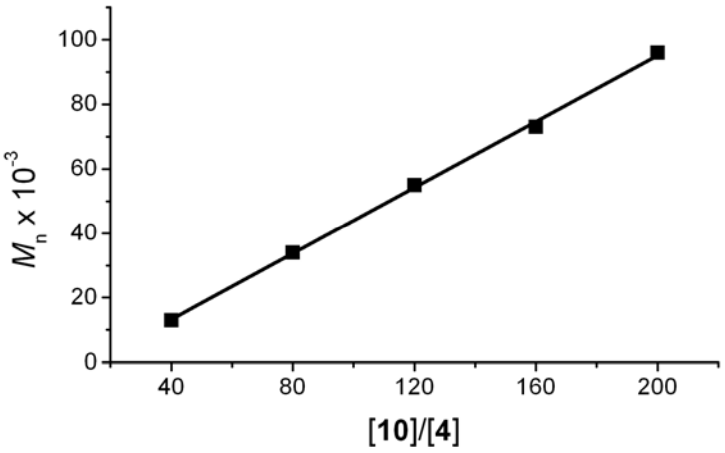


Figure 4.2. Plot of M_n vs monomer **10**/initiator **4** ratios for polymer **12a-e**.

Table 4.1. Polymer characterization data (GPC) for **12a-e**.[a]

Polymer	[M]/[I]	M_n	M_w	PDI
12a	40	13 000	20 000	1.56
12b	80	34 000	43 000	1.27
12c	120	55 000	68 000	1.23
12d	160	73 000	88 000	1.20
12e	200	96 000	114 000	1.19

[a] M_n = number-average molecular weight; M_w = weight-average molecular weight; PDI = polydispersity index.

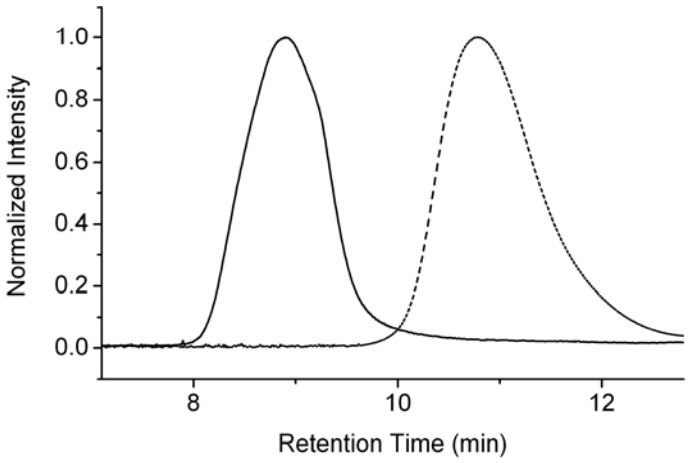
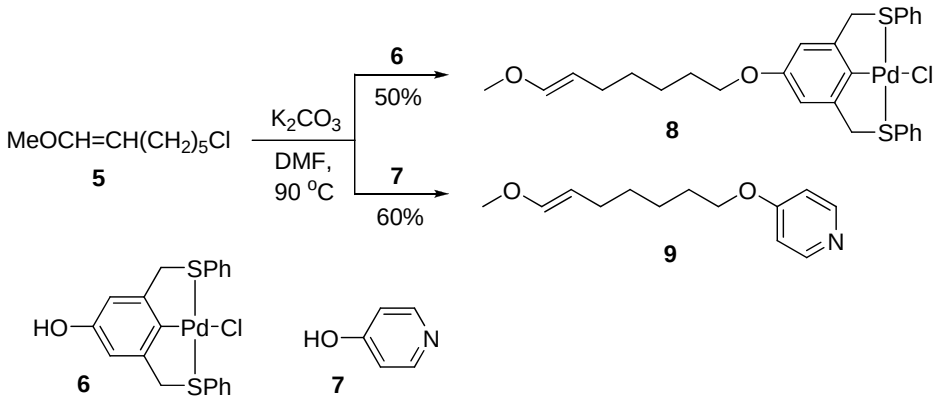


Figure 4.3. GPC traces of homoblock copolymers obtained from **10** using **4**. Dashed line: polymer after complete conversion of the monomer ([M]/[I] = 40:1, M_n = 13 000, PDI = 1.56). Solid line: polymer after standing for 2 h and then continued polymerization of the additional monomer ([M]/[I] = 1 000:1, M_n = 258 000, PDI = 1.25).

4.4.3 Chain-Terminator Synthesis

Any desired terminal functionality can be installed in living ROMP through the use of functionalized vinyl ether derivatives that serve as chain-terminators, *i.e.* they terminate the polymerization by incorporating the desired functionality at the polymer chain-end.[9] To install supramolecular functionalities for metal coordination at both chain-ends of the polymer, SCS-Pd(II) pincer- and pyridine-based CTs were synthesized as outlined in Scheme 4.2. 6-Chloro-1-hexenyl methyl ether **5** was reacted with SCS-Pd(II) pincer precursor **6** or 4-hydroxypyridine **7** using Williamson etherification to afford CTs **8** and **9**, respectively.

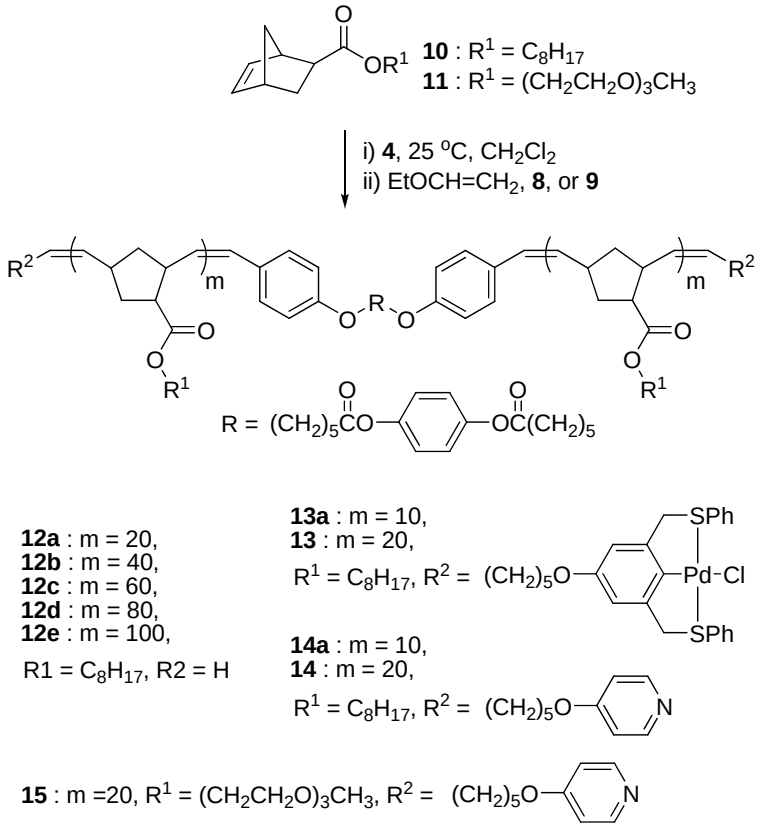
Scheme 4.2. Synthesis of CTs **8** and **9**.



4.4.4 Telechelic Polymer Synthesis

ROMP of norbornene octyl ester **10** (for **13** and **14**) or norbornene methyltriglycol ester **11** (for **15**) was carried out with 2.5 mol% of **4** in CH_2Cl_2 followed by the addition of an excess of either **8** to obtain SCS-Pd(II) pincer-functionalized telechelic polymer **13** or **9** to yield pyridine-functionalized telechelic polymers **14** and **15** (Scheme 3). Complete termination of the ROMP was observed by the disappearance of the polymeric carbene signals in the ^{1}H NMR spectra. Complete incorporation of each functionality at both the chain-ends of each telechelic polymer was confirmed by ^{1}H NMR analysis. The molecular weights and PDIs of all the telechelic polymers were determined by GPC analyses revealing monomodal distributions (M_n = 14 000, PDI = 1.62 for **13**, M_n = 13 000, PDI = 1.57 for **14**, and M_n = 18 000, PDI = 1.51 for **15**). Thus the described methodology allows for full control over end group functionalization compared to the CTA-based ROMP in the preparation of symmetrical ditelechelic polymers.[5]

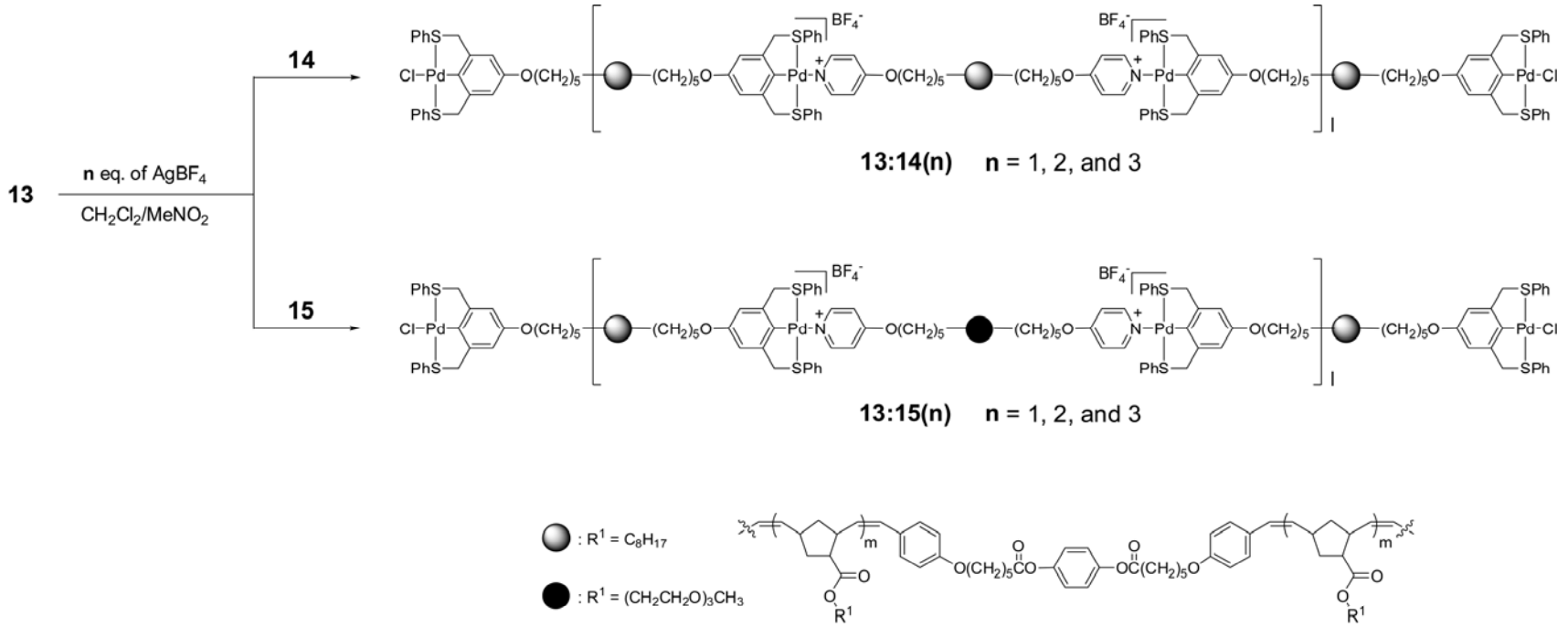
Scheme 4.3. Synthesis of telechelic polymers **12-15**.



4.4.5 Self-Assembly

The formation of supramolecular multiblock copolymers was investigated *via* metal coordination using telechelic polymers **13**–**15**. $AgBF_4$ is known to remove the Cl ligand on pincer complexes generating a cationic Pd species that can coordinate pyridyl units resulting in the formation of new pincer complexes.[8] By controlling the ratio of $AgBF_4$ in the mixture of complementary telechelic polymers to activated Pd-pincer moieties one should be able to control the length of supramolecular block copolymers formed by metal coordinaiton.

Scheme 4.4. Self-assembly of telechelic polymers **13-15**.



The preparation of supramolecular homoblock copolymers (SHBCs) **13:14(n)** and supramolecular alternating block copolymers (SABCs) **13:15(n)** is outlined in Scheme 4.4. SABCs **13:15(n)** are based on two chemically different blocks, octyl- and methyltriglycol-substituted poly(norbornene)s, which may result in phase separation of individual blocks whereas the constituent blocks in SHBCs **13:14(n)** should be completely miscible. **13:14(n)** and **13:15(n)** were synthesized by the addition of **n** equivalents (**n** = 1, 2, or 3) of $AgBF_4$ to a solution of 1 equivalent of **13** and 1 equivalent of **14** or **15**, respectively. The formation of supramolecular block copolymers was characterized by ^{1}H NMR spectroscopy, Ubbelohde viscometry, and dynamic light scattering (DLS).

Telechelic polymers **13a** and **14a** were employed for the metal coordination because shorter 20 mers allow for easy ^{1}H NMR spectroscopy characterization. SHBC **13a:14a** was prepared by the addition of 3 equivalents of $AgBF_4$ to a solution of 1 equivalent each of **13a** and **14a** in dichloromethane. The formation of SHBC **13a:14a** was confirmed from charcteristic shifts in the ^{1}H NMR spectrum. Figures 4.4.A and 4.4.B show the ^{1}H NMR spectra of **13a** and **14a**, respectively. Figure 4.4.C displays a mixture of **13a** and **14a** at a 1:1 ratio; no shifts in the ^{1}H NMR spectra are observed. Upon addition of $AgBF_4$, the resulting ^{1}H NMR spectrum of SHBC **13a:14a** shows the characteristic downfield shifts of the α- and β-pyridyl signals from 7.23 (α) and 6.23 (β) ppm to 7.96 (α') and 7.29 (β') ppm, respectively. In addition to the diagnostic shifts of the pyridyl signals, the aromatic proton signals on the pincer complex broaden and shift slightly from 7.79, 7.36, and 6.63 ppm to 7.74, 7.44, and 6.58 ppm, respectively (Figure

4.4.D). These characteristic shifts indicate quantitative metal coordination between **13a** and **14a**, resulting in the formation of SHBC **13a:14a**.

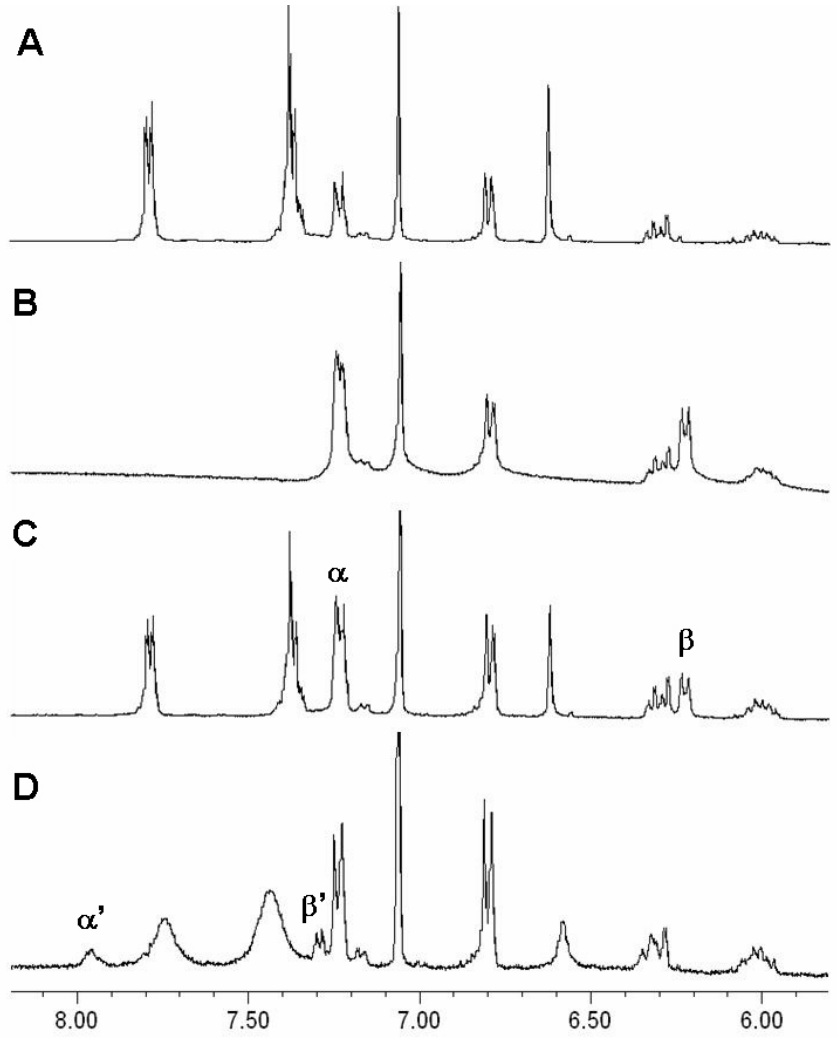


Figure 4.4. ^{1}H NMR spectra depicting metal coordination of **13a** with **14a** in CD_2Cl_2. A) Telechelic polymer **13a**; B) telechelic polymer **14a**; C) a mixture of telechelic polymers **13a** and **14a** at a 1:1 ratio: α and β = α- and β-pyridyl protons, respectively; D) self-assembled telechelic polymer **13a:14a** after addition of $AgBF_4$: α' and β' = α- and β-pyridyl protons on pyridyl pincer complex, respectively.

Viscometry is a simple yet powerful technique to demonstrate the formation of supramolecular multiblock polymers.[4a,5b,10] The solution properties of SHBCs **13:14(n)** and SABCs **13:15(n)** in dichloromethane were examined by viscometry, and the results are shown in Figure 4.5. The specific viscosity (η_{sp}) of both SHBCs **13:14(n)** and SABCs **13:15(n)** increases as the equivalence of $AgBF_4$ increases from 1 to 2 to 3. Additionally, the relatively slight increases from SHBC **13:14(2)** and SABC **13:15(2)** to SHBC **13:14(3)** and SABC **13:15(3)**, respectively, represent that 2 equivalents of $AgBF_4$ are sufficient for efficient metal coordination leading to the formation of supramolecular block copolymers. Compared with SHBCs **13:14(n)**, SABCs **13:15(n)** show much larger η_{sp} values probably due to, at least partial, phase separation of the two different blocks. As a control experiment, we also carried out viscometry experiments on a 1:1 mixture of pyridine-functionalized telechelic polymer **15** and unfunctionalized polymer **12a** before and after the addition of $AgBF_4$. The η_{sp} values after addition of $AgBF_4$ were unchanged supporting our hypothesis that the increase in η_{sp} values is the direct result of the formation of supramolecular alternating block copolymers.

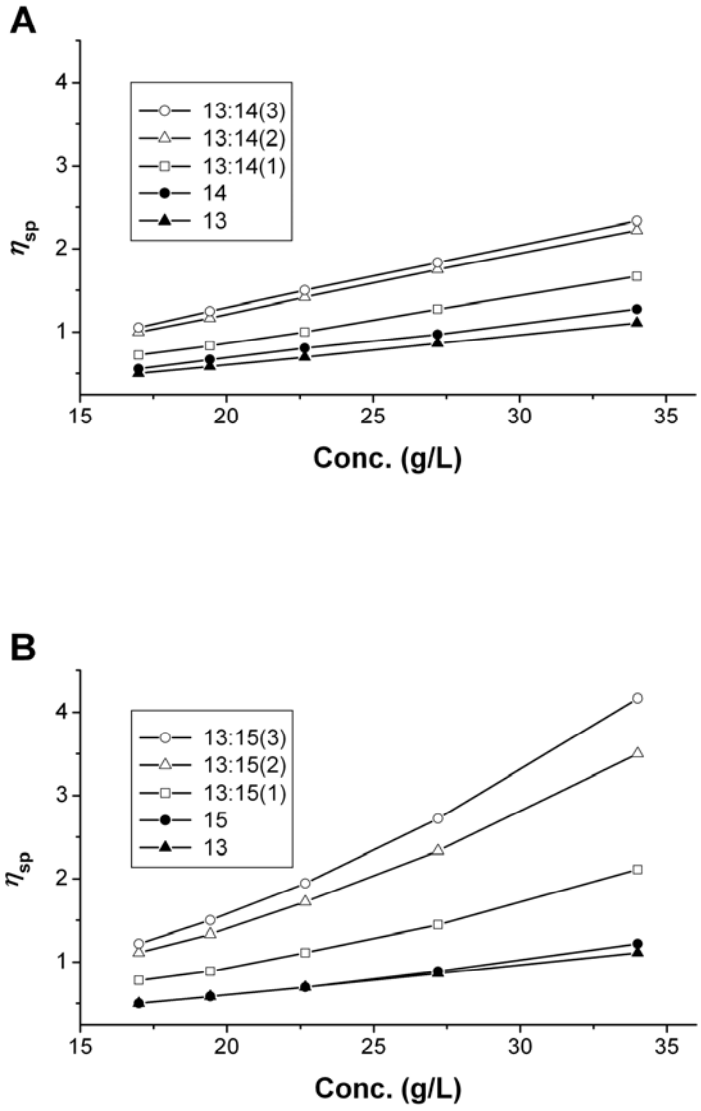


Figure 4.5. Specific viscosity (η_{sp}) at 25 °C in CH_2Cl_2. A) Telechelic polymers **13** and **14**, and SHBCs **13:14(n)** after addition of n equiv of $AgBF_4$; B) telechelic polymers **13** and **15**, and SABCs **13:15(n)** after addition of n equiv of $AgBF_4$.

To examine the bulk structure of SHBCs **13:14(n)** and SABCs **13:15(n)** in more detail, the hydrodynamic radii (R_h) of these materials were determined by DLS (Table 4.2). The particle size for both classes of materials increases with increased equivalence of $AgBF_4$ from 1 to 2 to 3, indicating that the polymeric block length can be tuned by the amount of $AgBF_4$ added. Also, a significant increase in size (almost two times) from 1 equivalent to 2 equivalents of $AgBF_4$ indicates the formation of supramolecular block copolymers. The fact that larger aggregates were observed in SABCs **13:15(n)** compared to SHBCs **13:14(n)**, suggests that the phase separation between the blocks results in increased hydrodynamic volume of SABCs with negligible effect on the metal coordination. Thus, the DLS data are consistent with the viscometry results strongly suggesting the formation of supramolecular multiblock copolymers.

Table 4.2. Hydrodynamic radius (R_h) of SHBCs **13:14(n)** and SABCs **13:15(n)** measured by DLS at 34 g/L (25 °C, CH_2Cl_2).

SHBC	R_h (nm)	SABC	R_h (nm)
13:14(1)	35.8	**13:15(1)**	66.8
13:14(2)	77.5	**13:15(2)**	119.3
13:14(3)	79.4	**13:15(3)**	142.0

4.5 Conclusion

In this chapter, a novel methodology for the synthesis of symmetrical telechelic polymers bearing terminal recognition motifs has been developed. A bimetallic ruthenium initiator was synthesized in a straight forward fashion *via* carbene exchange and used for the incorporation of supramolecular functionalities onto polymer chain-ends. The hydroquinone phenyl ring in the ruthenium initiator offers an opportunity to introduce stimuli-responsive functionalities in the middle of the polymeric backbone. Such functionalities could render these block copolymers pH cleavable or light responsive. Further, termination of the living ROMP with functionalized CTs afforded the symmetrical telechelic polymers in a single step. Self-assembly of the telechelic polymers to afford block copolymers was achieved by metal coordination between recognition units. The formation of supramolecular block copolymers was substantiated using ^{1}H NMR spectroscopy, viscometry, and DLS.

4.6 Experimental

All reagents were purchased either from Acros Organics, Alfa Aesar, or Sigma-Aldrich and used without further purification unless otherwise noted. CH_2Cl_2 was dried *via* passage through copper oxide and alumina columns. NMR spectra were recorded using a Bruker AV-400 (^{1}H: 400.1 MHz; ^{13}C: 100.6 MHz) spectrometer. Chemical shifts are reported in ppm and referenced to the corresponding residual nuclei in deuterated solvents. Elemental analyses were performed using a Carlo Erba 1108 elemental analyzer. Mass spectral analyses were provided by the Georgia Tech Mass Spectrometry Facility using a VG-70se spectrometer. Viscosity was measured in dichloromethane using a

Cannon semi-micro Ubbelohde viscometer (9722-G59) at 25 °C. The hydrodynamic radius (R_h) was measured using a Protein Solutions DLS (DynaPro) at 25 °C and analyzed with a Dynamics V6 software. Gel-permeation chromatography (GPC) analyses were carried out using a Shimadzu pump coupled to a Shimadzu UV detector with tetrahydrofuran (THF) as the eluant and a flow rate of 1 mL/min on American Polymer Standards column set (100, 1000, 100 000 Å, linear mixed bed). All GPCs were calibrated using poly(styrene) standards and carried out at 25 °C. M_w, M_n, and PDI represent the weight-average molecular weight, number-average molecular weight, and polydispersity index, respectively. 6-(4-Vinylphenoxy) hexanoic acid **1**,[10] 6-chloro-1-hexenyl methyl ether **5**,[9b] SCS-Pd(II) pincer precursor **6**,[11] and monomers **10** and **11**[12] were synthesized according to the previously published procedures.

Bis-styrene 2. To a solution of 6-(4-vinylphenoxy) hexanoic acid **1** (0.59 g, 2.5 mmol) and hydroquinone (0.13 g, 1.2 mmol) in anhydrous DMF (8 mL) were added *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (0.55 g, 2.9 mmol) and 4-dimethylaminopyridine (17 mg, 0.14 mmol). After the mixture was stirred at 25 °C for 6 h, the solvent was removed under reduced pressure. Water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a yellow oil that was further purified by column chromatography on silica gel in dichloromethane to yield 0.59 g of a white solid in 96% yield. ^{1}H NMR ($CDCl_3$): δ 7.34 (d, J = 8.8 Hz, 4H), 7.09 (s, 4H), 6.85 (d, J = 8.8 Hz, 4H), 6.66 (dd, J = 17.6, 11.0 Hz, 2H), 5.61 (d, J = 17.6 Hz, 2H), 5.12 (d, J = 11.0 Hz, 2H), 3.99 (t, J = 6.4 Hz, 4H), 2.60 (t, J = 7.6 Hz, 4H), 1.83 (m, 8H), 1.61 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 171.9, 158.8, 148.1,

136.3, 130.4, 127.4, 122.4, 114.5, 111.5, 67.6, 34.2, 28.9, 25.6, 24.6. Anal. Calcd for $C_{34}H_{38}O_6$: C, 75.25; H, 7.06. Found: C, 74.81; H, 7.03. ESI-MS *m*/*z*: calcd for $C_{34}H_{38}O_6$, 542.2688; found, 543.2741 $[M+H]^+$.

Bis-ruthenium initiator 4. Bis-styrene **2** (0.10 g, 0.18 mmol) and Grubbs' first-generation initiator **3** (0.60 g, 0.73 mmol) were dissolved in anhydrous, degassed CH_2Cl_2 (10 mL) under an argon atmosphere and stirred at 25 °C for 1 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexanes/EtOAc (4:1)) to yield 0.26 g of a purple solid in 72% yield. ^{1}H NMR (CD_2Cl_2): δ19.44 (s, 2H), 8.41 (br, 4H), 7.07 (s, 4H), 6.79 (d, J = 8.8 Hz, 4H), 4.01 (t, J = 6.4 Hz, 4H), 2.58 (m, 16H), 1.94-1.12 (m, 132H). ^{13}C NMR (CD_2Cl_2): δ290.6, 172.3, 160.0, 148.6, 148.2, 134.3, 122.8, 114.4, 68.3, 34.5, 32.4, 30.0, 29.2, 28.3, 27.0, 25.9, 25.0. Anal. Calcd for $C_{104}H_{166}O_6Cl_4P_4Ru_2$: C, 63.08; H, 8.45. Found: C, 62.53; H, 8.42.

CT 8. To a solution of 6-chloro-1-hexenyl methyl ether **5** (0.20 g, 1.2 mmol) and SCS-Pd(II) pincer precursor **6** (0.60 g, 1.3 mmol) in anhydrous DMF (10 mL) was added potassium carbonate (0.52 g, 3.8 mmol). After the mixture was stirred at 90 °C for 12 h, the solvent was removed under reduced pressure. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexanes/EtOAc (2:1)) (0.38 g, 50%). ^{1}H NMR ($CDCl_3$): δ7.79 (dd, J = 7.2, 2.0 Hz, 4H), 7.36 (m, 6H), 6.63 (s, 2H), 6.28 (d, J = 12.4 Hz, 0.6H), 5.87 (d, J = 6.4 Hz, 0.4H), 4.70 (td, J = 12.4, 7.6 Hz, 0.6H), 4.64 (br, 4H), 4.33 (dd, J = 7.2, 6.4 Hz, 0.4H), 3.88 (t, J = 6.4 Hz, 2H), 3.57 (s, 1.2H),

3.50 (s, 1.8H), 2.08 (m, 0.8H), 1.94 (m, 1.2H), 1.75 (m, 2H), 1.41 (m, 4H). ^{13}C NMR ($CDCl_3$): δ226.8, 157.2, 149.8, 147.2, 146.2, 132.8, 131.7, 129.8, 129.6, 108.0, 106.6, 102.8, 68.1, 59.5, 55.9, 54.5, 30.4, 29.5, 29.2, 27.6, 25.7, 25.4, 23.8. ESI-MS *m*/*z*: calcd for $C_{28}H_{31}ClO_2PdS_2$, 604.0489; found, 569.0800 $[M\text{-}Cl]^+$.

CT 9. Potassium carbonate (1.4 g, 10 mmol) was added to a solution of 6-chloro-1-hexenyl methyl ether **5** (0.55 g, 3.4 mmol) and 4-hydroxypyridine **7** (0.35 g, 3.7 mmol) in anhydrous DMF (10 mL). After the mixture was stirred at 90 °C for 12 h, the solvent was removed under reduced pressure. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (dichloromethane/methanol (15:1)) (0.45 g, 60%). ^{1}H NMR ($CDCl_3$): δ7.25 (d, J = 8.0 Hz, 2H), 6.36 (d, J = 8.0 Hz, 2H), 6.26 (d, J = 12.0 Hz, 0.6H), 5.86 (d, J = 6.4 Hz, 0.4H), 4.65 (td, J = 12.0, 7.2 Hz, 0.6H), 4.33 (dd, J = 7.0, 6.4 Hz, 0.4H), 3.73 (t, J = 7.2 Hz, 2H), 3.55 (s, 1.2H), 3.48 (s, 1.8H), 2.04 (m, 0.8H), 1.91 (m, 1.2H), 1.75 (m, 2H), 1.35 (m, 4H). ^{13}C NMR ($CDCl_3$): δ147.5, 146.6, 139.5, 139.5, 118.8, 105.8, 102.2, 59.5, 57.0, 56.9, 56.0, 30.7, 30.5, 30.1, 28.9, 27.3, 25.5, 25.4, 23.3. EIMS *m*/*z*: calcd for $C_{13}H_{19}NO_2$, 221.1416; found, 221.1413.

General polymerization procedure. The desired amount of monomer was dissolved in anhydrous, degassed CH_2Cl_2 under an argon atmosphere. Bis-ruthenium initiator **4** was added as a solution in the corresponding solvent. Upon complete polymerization, ethyl vinyl ether (for **12**), CT **8** (for **13**), or CT **9** (for **14** and **15**) was added to quench the polymerization. The polymer was isolated and purified by repeated precipitations into MeOH (for **12-14**) or diethyl ether (for **15**).

Self-assembly studies. Polymer **13** was dissolved in CD_2Cl_2 and polymer **14** or **15** was added until a 1:1 equivalency was reached in relation to the Pd-pincer complexes as determined by ^1H NMR spectroscopy. The desired amount of $AgBF_4$ dissolved in $MeNO_2$ was added to the reaction mixture. After stirring at 25 °C for 4 h, the precipitated AgCl(s) was removed by centrifugation. The supernatant liquid was filtered through a plug of Celite and subsequently through a 0.2 μm syringe filter. The solvent was removed *in vacuo* to yield the supramolecular block copolymers.

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CHAPTER 5

SUPRAMOLECULAR ABC TRIBLOCK COPOLYMERS

5.1 Abstract

A Hamilton receptor- and DAN-functionalized heterotelechelic poly(norbornene imide) was synthesized *via* ROMP through a combination of a Hamilton receptor-functionalized ruthenium initiator and a diamidonaphthyridine-based chain-terminator. Furthermore, two cyanuric acid- or ureidoguanosine-terminated monotelechelic polymers were synthesized by the termination of ROMP of norbornene octyl ester with a cyanuric acid-based chain-terminator and the esterification of carboxylated poly(ethylene oxide) with hydroxy-containing ureidoguanosine, respectively. Complete incorporations of the supramolecular functionalities in the polymer chain-ends were confirmed by ^{1}H NMR spectroscopy. The telechelic polymers were self-assembled into ABC triblock copolymer through either stepwise or one-pot orthogonal strategies. ^{1}H NMR spectroscopy was used to monitor the self-assembly processes and revealed quantitative and orthogonal hydrogen bonding of the Hamilton receptor-cyanuric acid and diamidonaphthyridine-ureidoguanosine in all cases, demonstrating the formation of the supramolecular ABC triblock copolymer. The resulting block copolymers were characterized by 2-D NOESY, isothermal titration calorimetry, and viscometry.

5.2 Introduction

Inspired by nature's use of highly specific and selective noncovalent interactions to create complex architectures in a simultaneous multistep self-assembly process, polymer chemists have tried to emulate these self-assembly processes leading to the field of supramolecular polymer chemistry.[1] The goal of introducing noncovalent interactions in synthetic polymers is to improve their versatility and obtain materials with novel properties.[2,3] Hydrogen bonding has been the most common noncoavlent interaction used in supramolecular chemistry because of its synthetic accessibility, directionality, and responsiveness to a variety of external stimuli such as solvent, pH, and temperature.[4] Among supramolecular polymers, block copolymers are of considerable interest as they combine the phase separation behavior of block copolymers with the responsiveness of supramolecular polymers. They are prepared by main-chain self-assembly of different, sometimes incompatible polymers with complementary recognition units at their chain-ends.[5] Most examples in the literature focus on the assembly of diblock and multiblock copolymers from monotelechelic and ditelechelic polymers, respectively.[6] In contrast, supramolecular ABC triblock copolymers have not been explored although these are promising candidates for new materials with unprecedented properties. The main reason for the lack of supramolecular ABC triblock copolymers in the literature is the difficulty of their preparation. A heterotelechelic polymer displaying two different recognition moieties is essential as the central block. Typically, post-polymerization functionalization reactions are needed to prepare such heterotelechelic building blocks and the introduction of two different, orthogonal supramolecular functionalities at the two ends of a polymer *via* this methodology is non-trivial.[7]

The Weck group recently reported the synthesis of a heterotelechelic polymer containing molecular recognition moieties in a single step without any post-polymerization modifications and further demonstrated the stepwise self-assembly of this heterotelechelic polymer to obtain a supramolecular ABC triblock copolymer for the first time (Figure 5.1).[8]

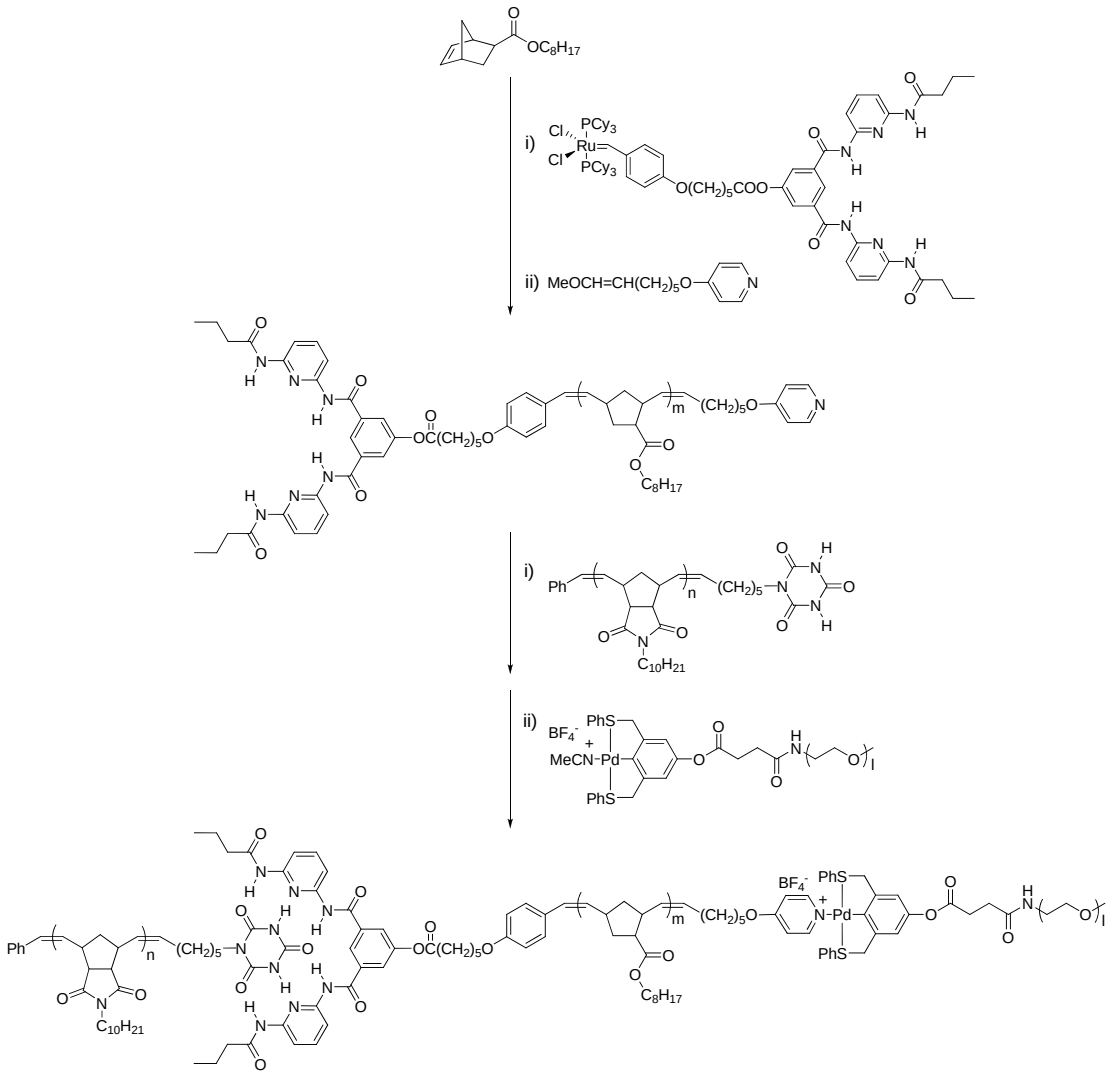


Figure 5.1. Synthesis of a heterotelechelic polymer using ROMP with functionalized initiators and chain-terminators and its self-assembly towards supramolecular ABC triblock copolymers.

The supramolecular interactions employed were the Hamilton receptor-cyanuric acid hydrogen bonding at one end and pyridine-palladated pincer metal coordination at the other end. However, due to incomplete orthogonality between the metal coordination and hydrogen bonding interactions used, the triblock copolymer could be self-assembled only by following a particular sequence beginning with the hydrogen bonding and ending with the metal coordination.

One goal that has not been accomplished is the use of two molecular recognition events that are completely orthogonal to each other. Then supramolecular ABC triblock copolymers could be obtained by simply adding three telechelic building blocks at once in a single pot. This will also allow for the attachment of either telechelic polymer (A or C block) to the middle B block first followed by the other giving rise to a library of block copolymeric structures with functional chain-ends (Figure 5.2). It was hypothesized that incorporating hydrogen bonding moieties at both chain-ends would be easier than introducing metal coordination units and the resulting supramolecular block copolymers would be more dynamic and stimuli-responsive systems. This chapter reports the realization of our goal by introducing the first one-pot synthesis of supramolecular ABC triblock copolymers *via* main-chain self-assembly of telechelic polymers using two distinct and orthogonal recognition events. This unique combination of orthogonal noncovalent interactions within polymeric systems represents an excellent tool for the synthesis of a new class of architecturally controlled supramolecular block copolymers.

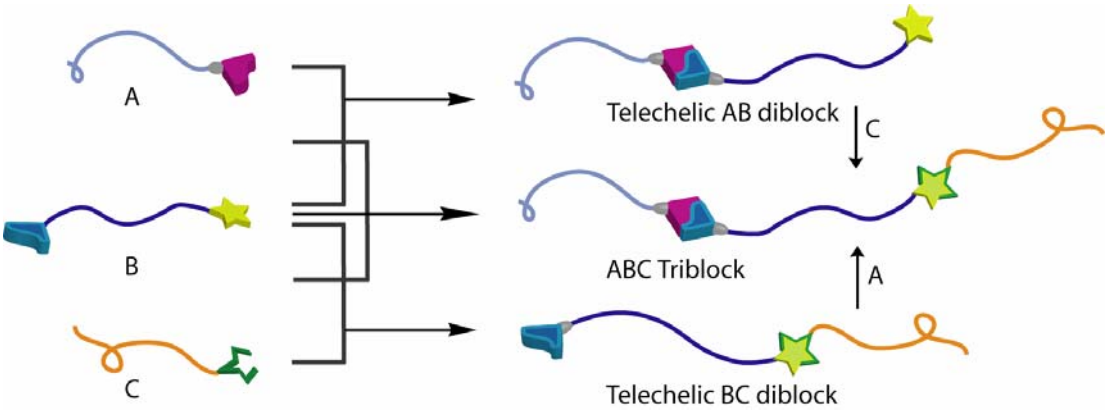


Figure 5.2. Schematic representation of the one-pot synthesis of a supramolecular ABC triblock copolymer.

5.3 Results and Discussion

In order to realize the traget self-assembly strategy towards ABC triblock copolymers, the recognition moieties to be installed at the chain-ends must meet certain criteria. Firstly, the two noncovalent interactions should have high association constants to hold the polymeric chains together. Second, the noncovalent interactions should be highly specific that is the two pairs should be completely orthogonal. Two distinct hydrogen bonding systems, the Hamilton wedge receptor-cyanuric acid (Wedge-CA) recognition pair and diamidonaphthyridine-ureidoguanosine (DAN-UG) recognition pair, were selected for the noncovalent interactions. The synthetic as well as supramolecular chemistry of these recognition pairs has been well established.[9,10] Both pairs display weak self-association as well as high association constants ($K_a \sim 10^5$ M^{-1} for Wedge-CA and $K_a \sim 10^7$ M^{-1} for DAN-UG). However, the orthogonality of these two recognition pairs has not been demonstrated before. It was hypothesized that the two recognition events could be independent of each other and the two chain-ends of the heterotelechelic

polymer could be addressed in an orthogonal fashion. This hypothesis was based on the fact that the pattern of the two hydrogen bonding arrays is completely different from each other. The 'wedge' displays a sextuple DAD-ADA pattern whereas the DAN-UG interaction is based on a quadruple DAAD-ADDA hydrogen bonding array. Thus, it is clear that any undesirable interaction between the Wedge/CA and DAN/UG pairs should be weak. Nevertheless, the selectivity between Wedge-CA and DAN-UG recognition pairs was first investigated using their small molecule analogues. To a mixture of the DAN and Hamilton receptor derivatives in dichloromethane, their respective complementary recognition units, UG and cyanuric acid derivatives, were added successively and the shift in the ^{1}H NMR signals of the amide protons was monitored using ^{1}H NMR spectroscopy (Figure 5.3). The chemical shifts of the amide protons of the two recognition pairs were equivalent to those found in control experiments where separate stoichiometric mixtures of Wedge-CA and UG-DAN were investigated. This was taken as the evidence for the orthogonality of both the hydrogen bonding interactions, i.e. no hydrogen bonding interaction between the two recognition pairs. These preliminary studies demonstrated that both Wedge-CA and DAN-UG recognition pairs could be used for the self-assembly of telechelic polymers to form supramolecular ABC triblock copolymers.

After establishing the orthogonal character of the recognition pairs, a Hamilton receptor- and DAN-functionalized heterotelechelic polymer was designed that should serve as the middle block of our ABC triblock copolymers to be self-assembled with two different cyanuric acid- and UG-terminated monotelechelic polymers to form the target polymers *via* the two orthogonal hydrogen bonding of the Wedge-CA and DAN-UG.

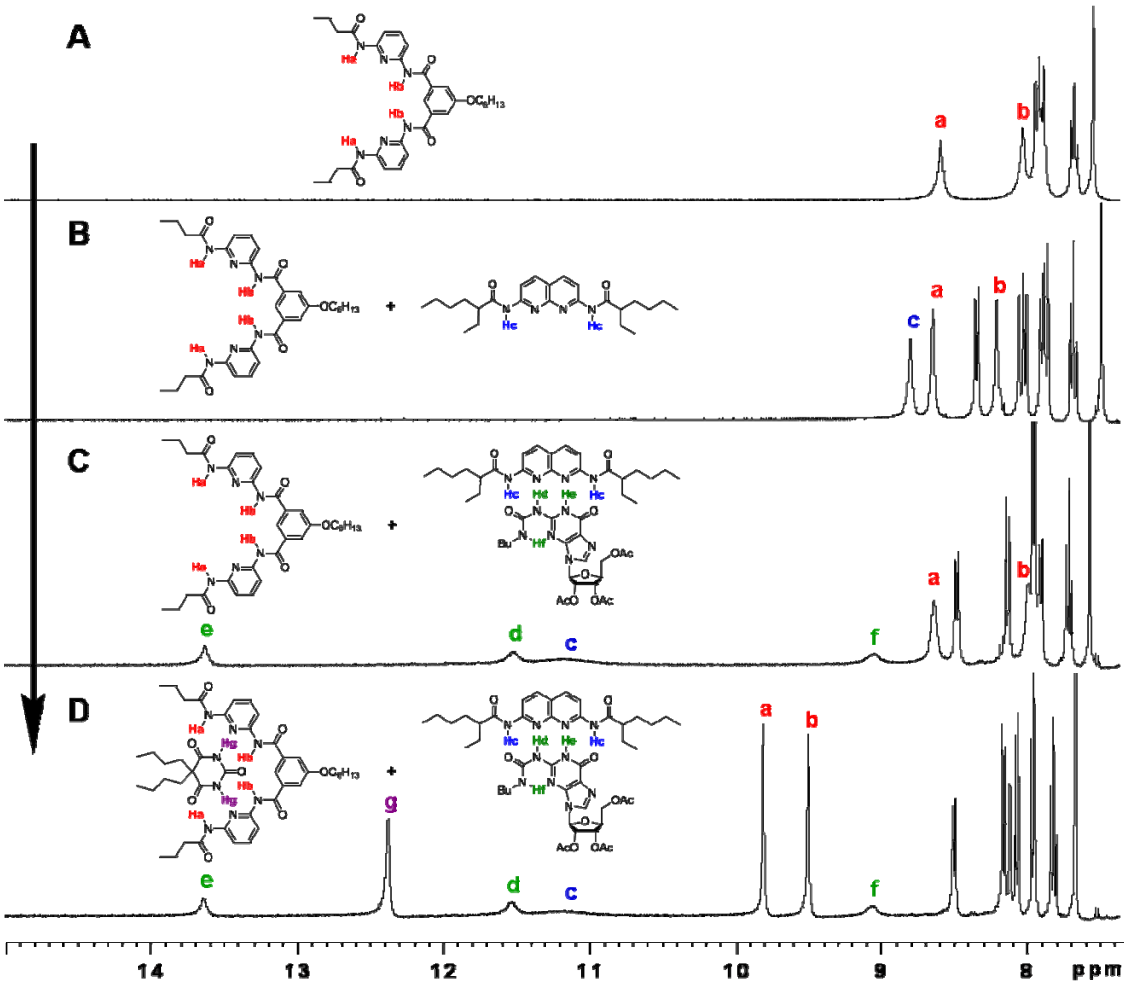


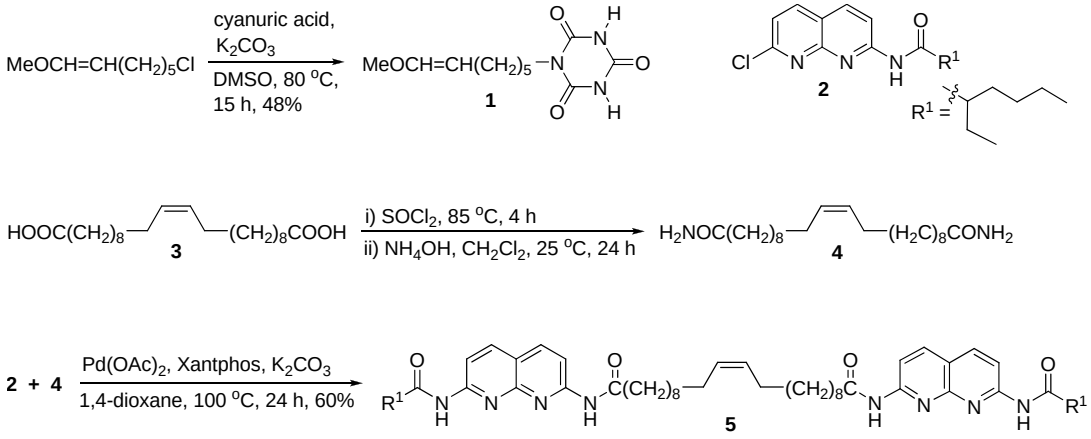
Figure 5.3. ^{1}H NMR spectra representing the orthogonal hydrogen bonding of Wedge-CA and DAN-UG derivatives in CD_2Cl_2.

5.3.1 Chain-Terminator Synthesis

Ring-opening metathesis polymerization (ROMP)[11] is the preferred synthetic method for the preparation of the telechelic polymers since living chain-ends can be terminated with functionalized chain-terminators (CTs) to install any desired functionality to the polymer chain-end. Functionalized vinyl ethers have been used as CTs to afford telechelic poly(norbornene)s in a single step.[12] To incorporate a hydrogen

bonding motif at the chain-end of the polymer, CA-based CT **1** was synthesized by reacting 6-chloro-1-hexenyl methyl ether with cyanuric acid. In ROMP of cyclic olefins, internal *cis*-olefins have been widely used as chain-transfer agents (CTAs) to afford symmetrical telechelic polymers by secondary metathesis.[13] When polymer repeat units are too bulky to undergo secondary metathesis, a *cis*-olefin can act instead as a CT to produce the monotelechelic polymer.[14] DAN-based CT **5** was designed due to its straightforward synthesis and efficient incorporation of the functionality at the polymer terminus.[6c] The synthetic pathway is outlined in Scheme 5.1. Dicarboxylic acid **3** was reacted with thionyl chloride to yield the corresponding diacyl chloride, which was subsequently converted to diamide **4** using concentrated ammonia. DAN-CT **5** was then obtained by Pd-catalyzed amidation of 7-amido-2-chloro-1,8-naphthyridine **2** with **4** in 1,4-dioxane.

Scheme 5.1. Synthesis of CTs **1** and **5**.



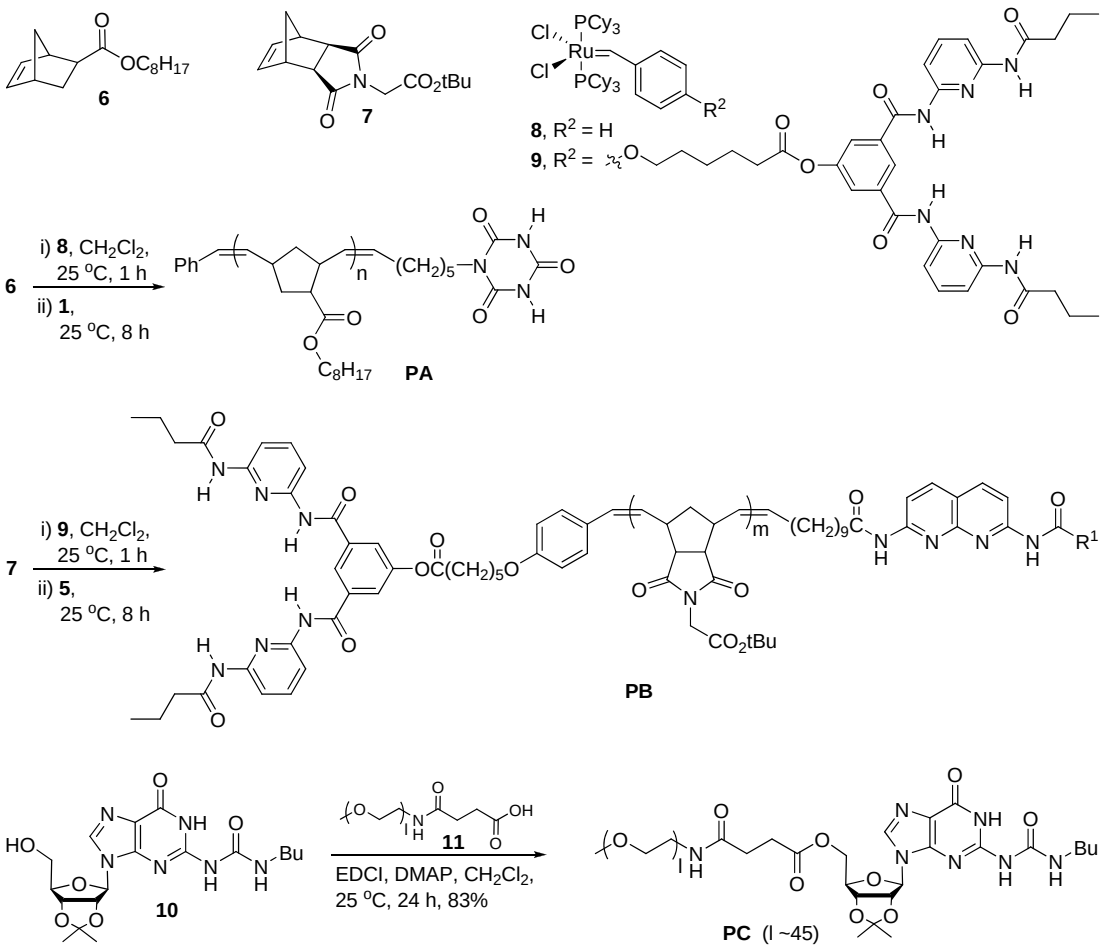
5.3.2 Telechelic Polymer Synthesis

The key to the supramolecular ABC triblock copolymers is the central heterotelechelic polymer containing two orthogonal recognition units. Such unsymmetrically end-functionalized polymers can be prepared in a single step when ROMP is initiated with a functionalized ruthenium initiator followed by termination with a functionalized CT. The Weck group has recently developed a Hamilton receptor-functionalized ruthenium initiator **9** that is not only active towards ROMP of norbornenes but affords living polymerization as well, allowing for the preparation of the heterotelechelic poly(norbornene)s through the combined use of a functionalized CT.[8] Sterically bulky *tert*-butyl ester norbornene imide monomer (tBENI) **7** was chosen as the backbone of the middle block for the ABC triblock copolymer to facilitate the incorporation of the second hydrogen bonding moiety from DAN-CT **5** onto the other chain-end of the polymer.[14] With the functionalized initiator **9** and CT **5** in hand, ROMP of monomer **7** was carried out with 5 mol% of **9** in CH_2Cl_2 to completion, followed by the addition of an excess of CT **5** to afford the targeted heterotelechelic polymer **PB** (Scheme 5.2). Complete initiation and termination were observed for the ROMP, resulting in complete incorporation of both end group functionalities in the polymer as confirmed by ^{1}H NMR analysis. The ^{1}H NMR spectrum of **PB** showed all characteristic signals for the Hamilton receptor and DAN moieties consistent with those observed in both small molecule analogues, indicating no interference of the two hydrogen bonding motifs with each other.

In addition to the central heterotelechelic poly(norbornene imide) **PB**, a CA-terminated poly(norbornene) **PA** and an UG-functionalized poly(ethylene oxide) (UG-

PEO) **PC** were employed for the other two blocks. Thus, all three blocks for the target ABC triblock copolymer consist of different polymeric backbones. The monotelechelic polymer **PA** was synthesized by ROMP of norbornene octyl ester **6** with 5 mol% of Grubbs' first-generation initiator **8** in CH_2Cl_2, followed by termination with CT **1** (Scheme 5.2). Complete termination of the ROMP was observed by the disappearance of the polymeric carbene signal in the ^{1}H NMR spectrum, allowing for near-quantitative end-functionalization. UG-PEO **PC** was prepared by EDCI-mediated esterification of carboxylated PEO **11** with UG **10** in CH_2Cl_2 (Scheme 5.2).[9] The molecular weights and polydispersity indices (PDIs) of **PA** and **PB** were determined by gel-permeation chromatography (GPC) traces which revealed monomodal distributions (M_n = 6 500, PDI = 1.30 for **PA**, and M_n = 6 500, PDI = 1.75 for **PB**; molecular weights are reported vs poly(styrene) standards).

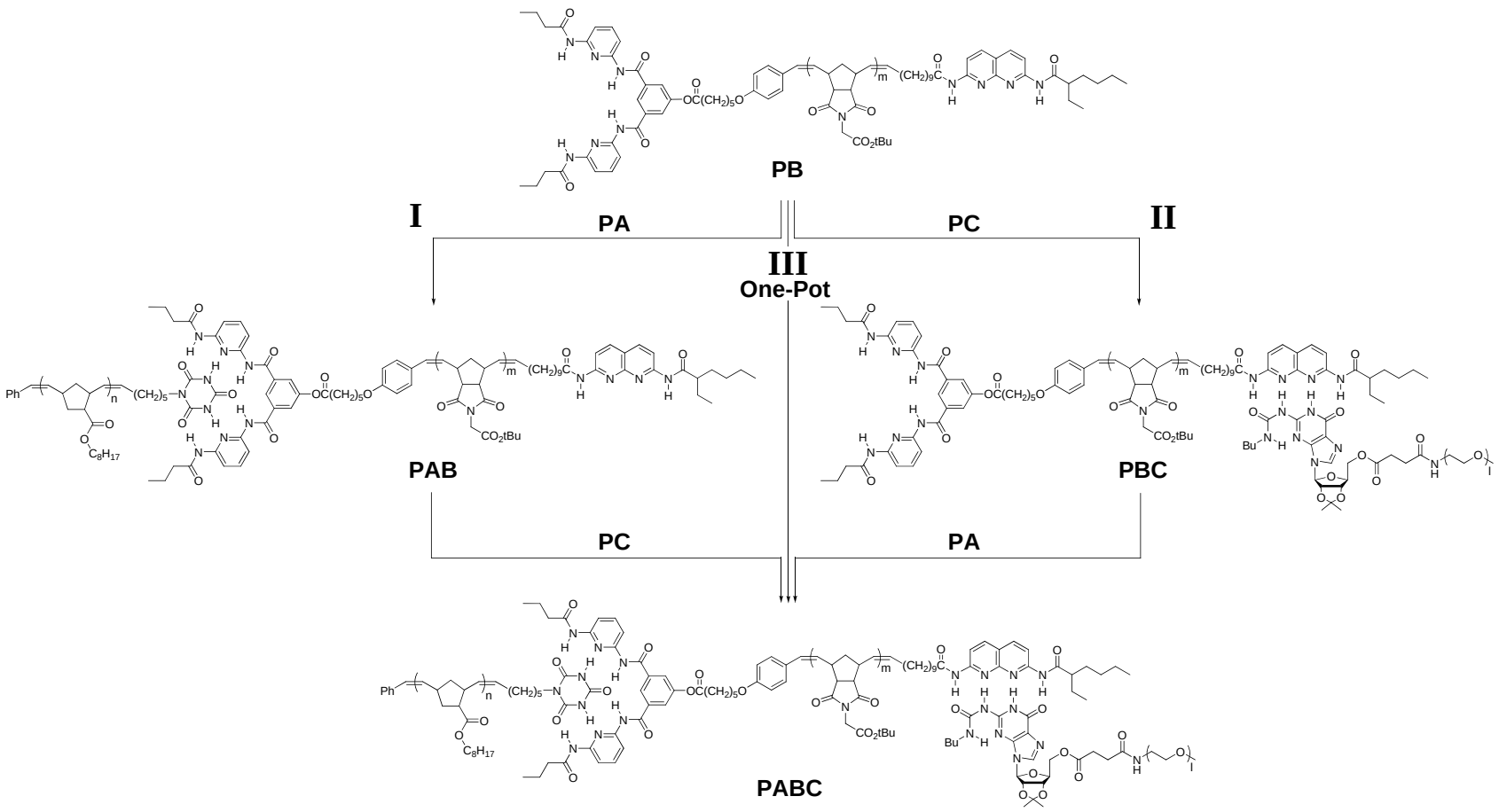
Scheme 5.2. Synthesis of Telechelic Polymers **PA**, **PB**, and **PC**.



5.3.3 ABC Triblock Copolymer Formation *via* Self-Assembly

The heterotelechelic polymer **PB** and monotelechelic polymers **PA** and **PC** provide the foundation for the formation of a supramolecular ABC triblock copolymer *via* main-chain self-assembly involving two different hydrogen bonding recognition processes. The self-assembly behavior of **PB** with **PA** and **PC** was examined by both stepwise and one-pot, orthogonal self-assembly strategies, as outlined in Scheme 5.3.

Scheme 5.3. ABC Triblock Copolymer Formation through Stepwise and One-Pot Self-Assembly.



To explore the versatility of the approach the self-assembly to form the targeted ABC triblock copolymer **PABC** was investigated in a stepwise fashion by two distinct routes - one beginning with hydrogen bonding between the Hamilton receptor and CA followed by DAN-UG hydrogen bonding (Scheme 5.3.I) and the other following the reverse order (Scheme 5.3.II). Both of these routes can be characterized by monitoring characteristic changes in chemical shifts of the amide protons by using ^{1}H NMR spectroscopy. Figure 5.4.A-C show the ^{1}H NMR spectra for the stepwise self-assembly of **PB** by route I, while Figure 5.4.C-E illustrate the change in chemical shifts for the self-assembly through route II beginning with DAN-UG and ending with Wedge-CA hydrogen bonding. First, upon the addition of 1 equivalent of **PA** to **PB**, a diblock copolymer **PAB** is formed. The ^{1}H NMR spectrum reveals complete shifts of the amide protons (a and b) of the Hamilton receptor from 8.82 and 8.07 ppm to 9.78 and 9.28 ppm, respectively and a new signal at 12.97 ppm (g) that corresponds to the bound cyanuric acid unit. Notably, no change in the signal at 8.19 ppm for the amide of the DAN moiety (c) (Figure 5.4.B) was observed. Subsequently, the addition of 1 equivalent of **PC** to **PAB** resulted in the complete shift of the amide proton (c) of the DAN from 8.19 ppm to 11.38-12.32 ppm. In addition, the signals of the Wedge-CA heterocomplex at 9.28 (b), 9.78 (a), and 12.97 ppm (g) remain unaffected, while new signals of the complexed UG at 9.26 (f), 11.56 (d), and 13.67 ppm (e) are observed in the ^{1}H NMR spectrum, which suggested the formation of the triblock copolymer **PABC** (Figure 5.4.A). All characteristic signals observed for the Wedge-CA and UG-DAN hydrogen bonding are consistent with those reported previously in the literature.[9,10] These results clearly

indicate selective self-assembly of **PB** with **PA** and **PC** *via* the stepwise route I, resulting in the successful formation of the supramolecular ABC triblock copolymer **PABC**.

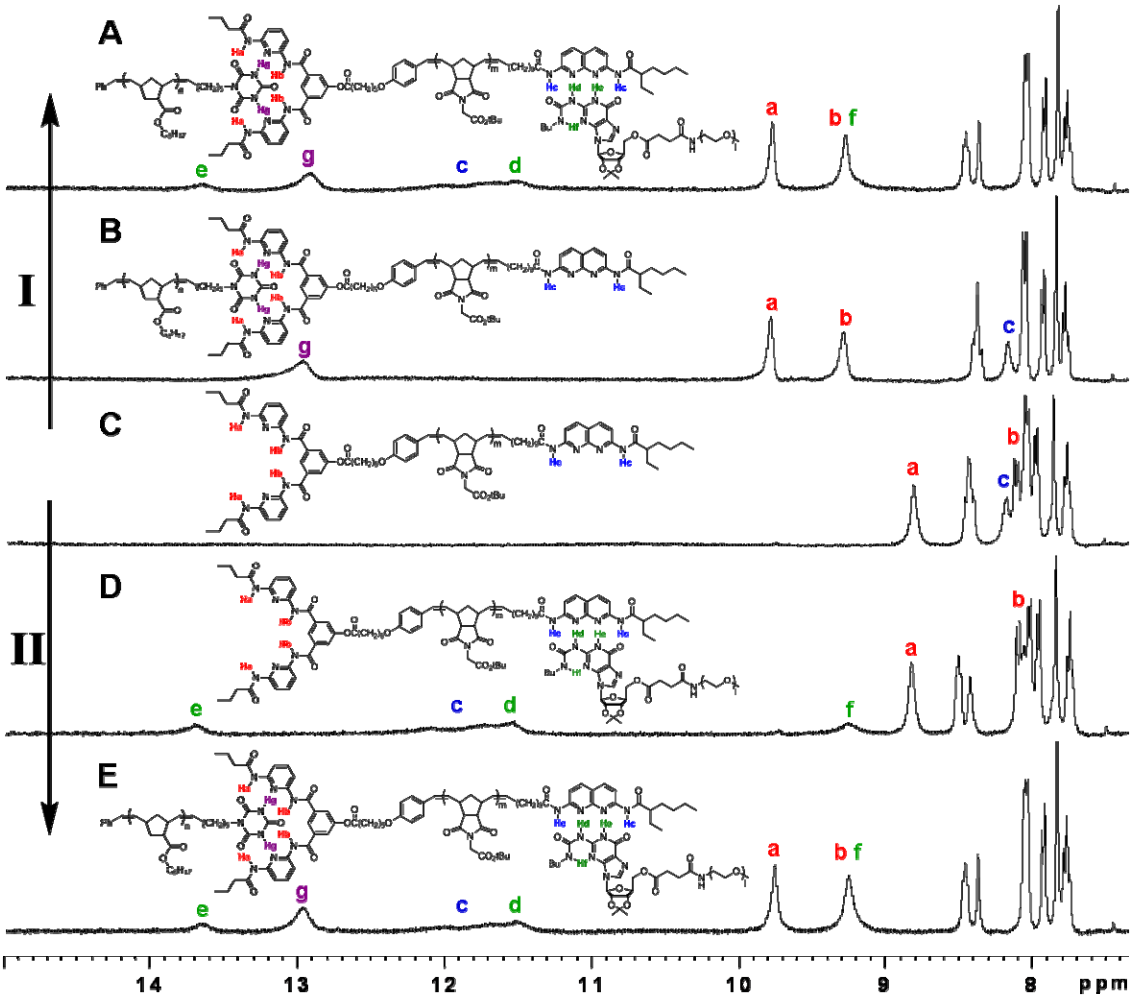


Figure 5.4. ^{1}H NMR spectra representing the stepwise self-assembly of **PB** with **PA** and **PC** in $CDCl_3$. ^{1}H NMR spectrum of (A) **PABC**, (B) **PAB**, (C) **PB**, (D) **PBC**, and (E) **PABC**.

Similarly, the formation of **PABC** through the stepwise route II was investigated using ^{1}H NMR spectroscopy. The NMR spectra obtained were compared with those from route 3I (Figure 5.4.A-C). Upon the addition of 1 equivalent of **PC** to **PB**, the same

characteristic shifts (c-f) for the DAN-UG complex as those shown in Figure 5.4.A are observed with no change in the signals for amide protons (a and b) of the unbound Hamilton receptor (Figure 5.4.D) suggesting the perfect orthogonality of both hydrogen bonding interactions. Subequently, the addition of 1 equivalent of **PA** to **PBC** allowed for the formation of fully self-assembled ABC triblock copolymer **PABC**, ^{1}H NMR spectrum of which (Figure 5.4.E) is identical to that in Figure 5.4.A. Thus, these ^{1}H NMR experiments demonstrate that the ABC triblock copolymer can be self-assembled starting from either chain-end of the B block and illustrate the versatility of our design.

It is necessary to quantify the strengths of the hydrogen bonding interactions to determine if the polymeric chains are indeed held together strongly - a necessary criterion for formation of supramolecular block copolymers. Therefore, the formation of **PABC** *via* the stepwise self-assembly was also investigated by isothermal titration calorimetry (ITC) experiments. Figure 5.5.A-B and 5.5.C-D show the binding isotherms for the stepwise self-assembly *via* the routes I and II, respectively. Association constants (K_a) for all stepwise self-assembly steps were determined by using a single-site binding model. The K_a for the CA-Wedge hydrogen bonding between **PA** and **PB** or **PBC** was found to be $1.5 \times 10^4 \pm 5\%$ M^{-1} and $1.4 \times 10^4 \pm 7\%$ M^{-1}, respectively, while the K_a for the UG-DAN hydrogen bonding between **PC** and **PB** or **PAB** was determined to be $2.0 \times 10^4 \pm 5\%$ M^{-1} and $1.7 \times 10^4 \pm 4\%$ M^{-1}, respectively. The K_a values for each of the recognition events are similar irrespective of the self-assembly route followed. The K_a values for CA-Wedge recognition are similar to those reported for polymeric systems.[8,15] The shapes of all the binding isotherms are also indicative of a strong interaction. These results

demonstrate that the two hydrogen bonding interactions are strong enough to hold the polymeric chains together despite the entropic penalty in polymeric systems.

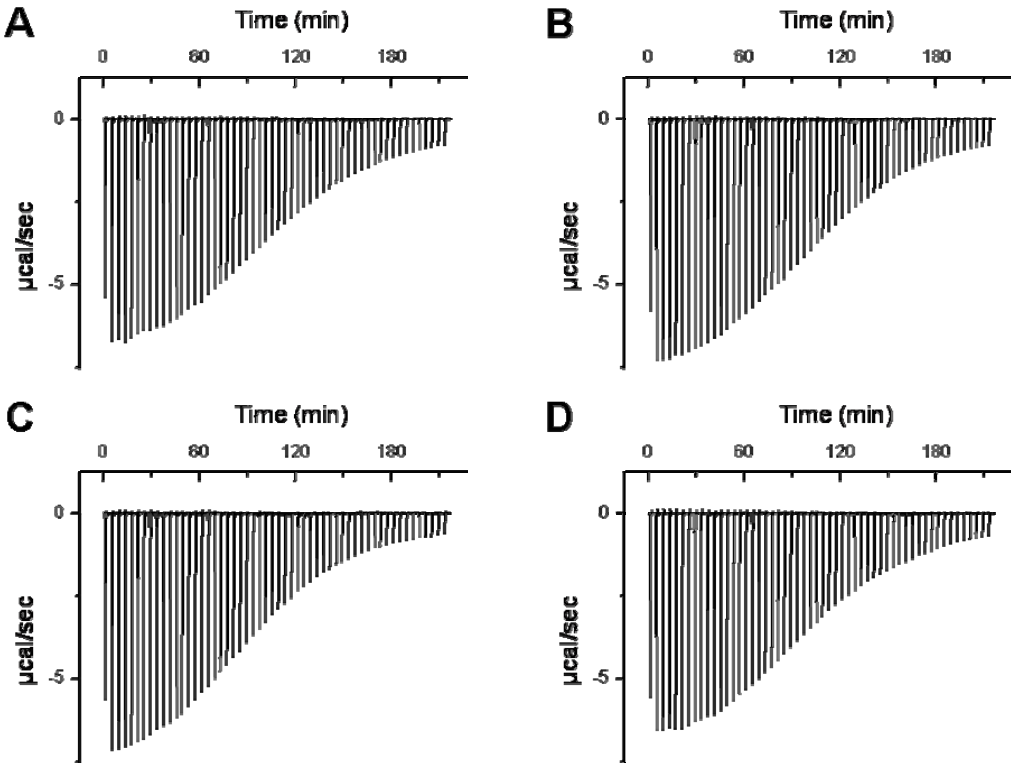


Figure 5.5. ITC binding isotherms for (A) **PA**-**PB**, (B) **PC**-**PAB**, (C) **PC**-**PB**, and (D) **PA**-**PBC** self-assembly in $CHCl_3$ at 30 °C.

To achieve the main goal - the preparation of the supramolecular ABC triblock copolymer *via* the one-pot self-assembly between two orthogonal hydrogen bonding recognition pairs - 1 equivalent of **PB** was added to a mixture of 1 equivalent each of **PA** and **PC** in $CDCl_3$. Figure 5.6.B shows the ^1H NMR spectrum of a mixture of **PA** and **PC** at a 1:1 ratio. Initially, no signal shifts are observed after the addition of **PA** to **PC**, suggesting no interaction between the two hydrogen bonding motifs, CA and UG. Upon

the addition of 1 equivalent of **PB** to the mixture, supramolecular triblock copolymer **PABC** is generated by the one-pot process. The ^{1}H NMR spectrum of **PABC** revealed all of the characteristic downfield shifts for the two recognition pairs: (1) CA (g, 8.63 ppm to 12.97 ppm) and the Hamilton receptor (a and b, 8.82 and 8.07 ppm to 9.81 and 9.31 ppm, respectively), and (2) DAN (c, 8.19 ppm to 11.38-12.32 ppm) and UG (e, d, and f, 12.11, 9.52, and 7.67 ppm to 13.67, 11.56, and 9.28 ppm, respectively) (Figure 5.6.C).

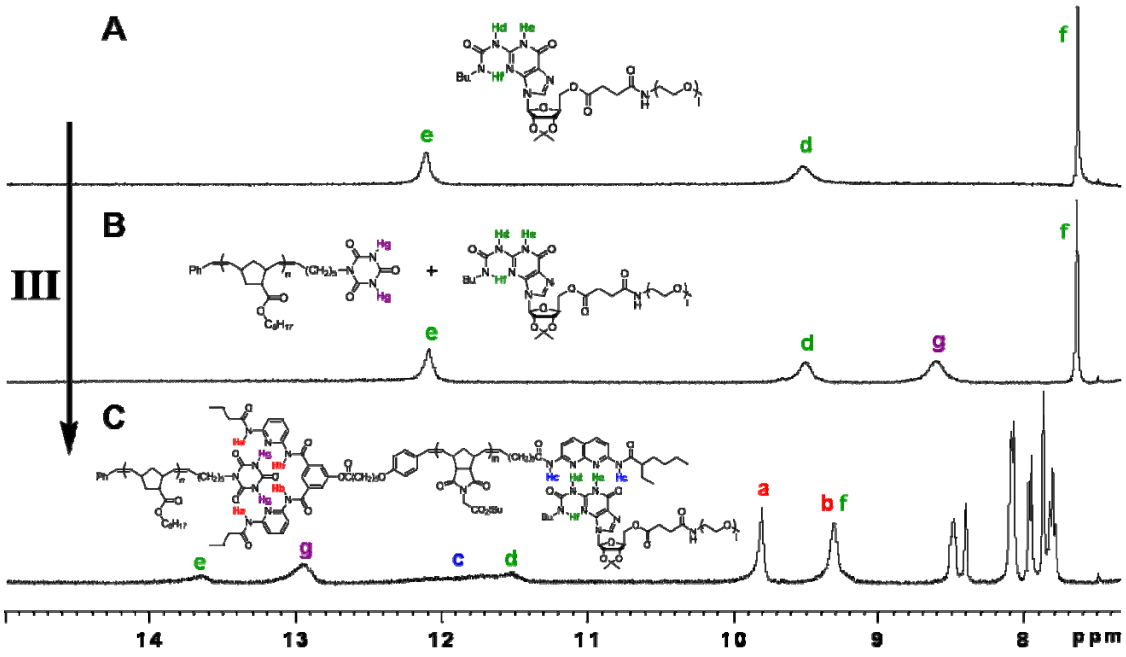


Figure 5.6. ^{1}H NMR spectra representing the one-pot self-assembly of **PB** with **PA** and **PC** in $CDCl_3$. (A) **PC**, (B) a mixture of **PA** and **PC** at a 1:1 ratio, and (C) **PABC**.

The final ^{1}H NMR spectrum of **PABC** by this one-pot process (Scheme 5.3.III) is identical to those obtained *via* the stepwise routes I and II, which demonstrates that the final fully supramolecular polymeric materials are identical, independent of the chosen self-assembly route. Thus, ^{1}H NMR spectroscopy provides strong evidence for the

formation of the supramolecular ABC triblock copolymer **PABC** *via* three different routes mediated by two strong and selective binding events between the complementary recognition units.

In addition to 1-D ^{1}H NMR, 2-D nuclear Overhauser effect spectroscopy (NOESY) was used to study the two orthogonal hydrogen bonding interactions involved in the formation of the supramolecular ABC triblock copolymer **PABC**. The NOESY spectrum of **PABC** generated by the one-pot process shows the signals for nuclear Overhauser effect interactions (NOEs) between the Hamilton receptor (a and b) and CA (g) protons, and between DAN (c) and UG (e) protons (Figure 5.7). The presence of signal for NOE between 'd' and 'f' protons of UG and absence of signal for NOE between 'c' and 'f' protons shows that UG is in a conformation that allows the quadruple hydrogen bonding recognition based on ADDA-DAAD pattern between UG and DAN. This result further indicates that the Hamilton receptor and DAN moietites of **PB** are indeed interacting with CA unit of **PA** and UG unit of **PC**, respectively, through hydrogen bonding recognition, resulting in the formation of **PABC**.

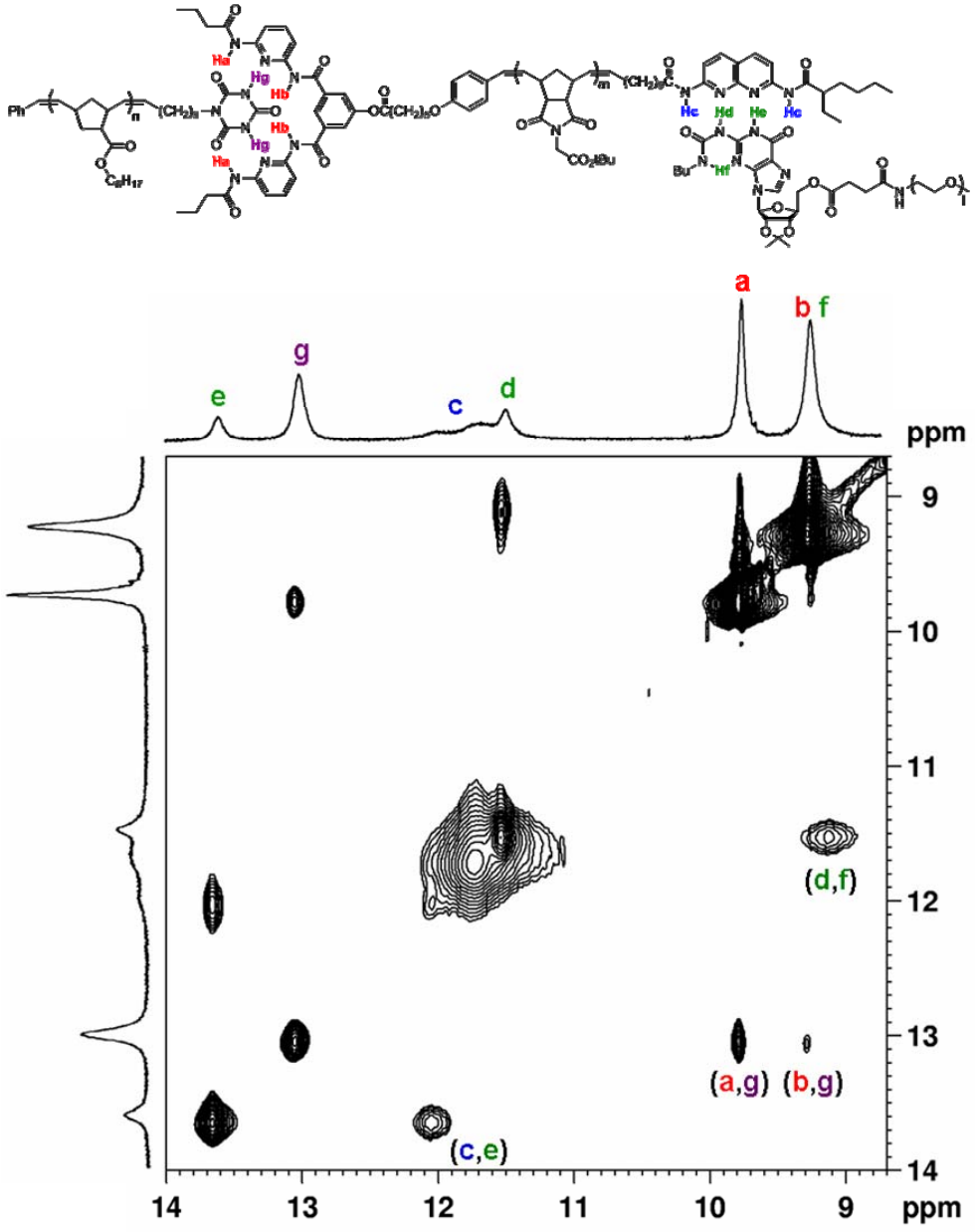


Figure 5.7. 2-D NOESY spectrum of **PABC** in $CDCl_3$ at 25 °C using 300 ms mixing time.

Upon the main-chain self-assembly through the complementary hydrogen bonding motifs, the high molecular weight species of the resulting supramolecular block copolymers should possess higher solution viscosity compared to that of their individual blocks. Thus, the self-assembled block copolymers in this study were further characterized by measuring their solution viscosity. The viscosity studies were carried out using an Ubbelohde viscometer in CH_2Cl_2 at 25 °C, and the results are shown in Figure 5.8. The specific viscosity (η_{sp}) increases from **PB** to **PBC** to **PAB** to **PABC**, which correlates with the increase in the estimated molecular weights of the self-assembled block copolymers. For example, even between the two diblock copolymers, the molecular weight of **PBC** is much lower than that of **PAB** because of a shorter PEO block and hence its η_{sp} values are closer to those of **PB** than to those of **PAB**. As a control experiment, viscosity studies by employing **PB** and unfunctionalized analogues of **PA** and **PC** (**uPA** and **uPC**, respectively) were carried out. The η_{sp} values of the mixture of **PB** with 1 equivalent each of **uPA** and/or **uPC** were nearly the same as that of **PB** or even slightly lower (Figure 5.9), suggesting that the increase in η_{sp} values is the direct result of the strong main-chain self-assembly between the constituent blocks. Therefore, in addition to ^{1}H NMR, 2-D NOESY, and ITC data, the solution viscosity results strongly suggest the formation of a supramolecular ABC triblock copolymer.

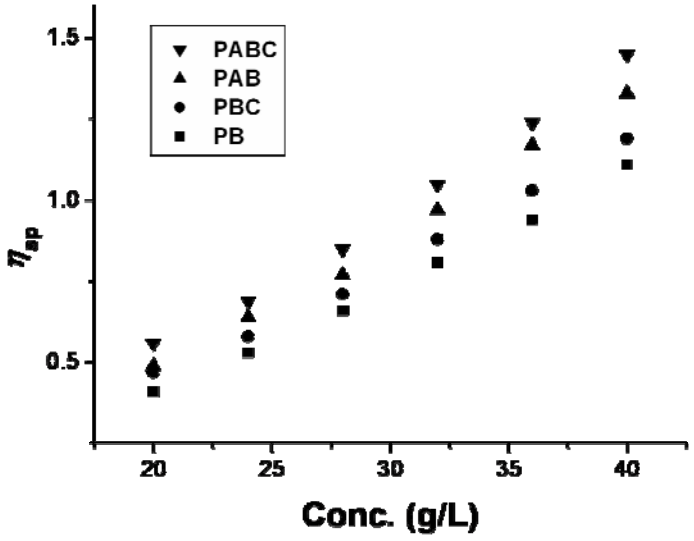


Figure 5.8. Plot of specific viscosity (η_{sp}) versus concentration for **PB** and block copolymers.

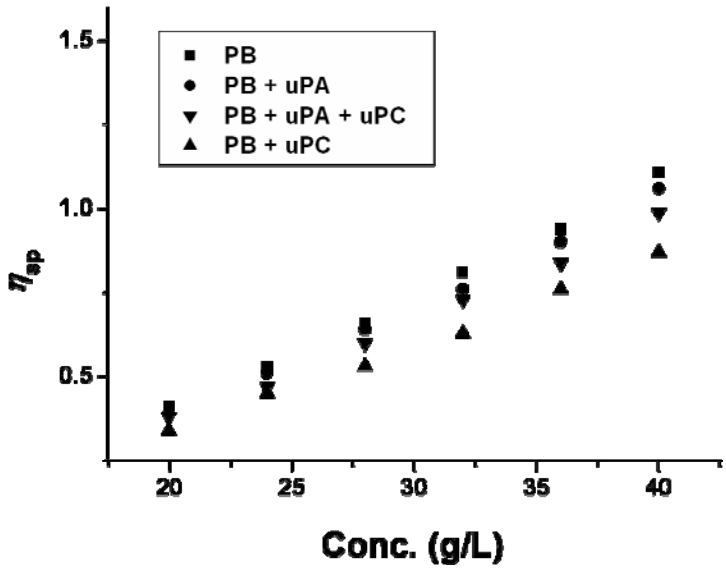


Figure 5.9. Plot of specific viscosity (η_{sp}) versus concentration for **PB** and its mixtures with **uPA** and/or **uPC**.

5.4 Conclusion

A novel methodology for the synthesis of supramolecular ABC triblock copolymers based on main-chain self-assembly of telechelic polymers using two different and orthogonal hydrogen bonding events has been developed. The key step for this methodology is the successful preparation of a heterotelechelic polymer possessing two different recognition moieties at the chain-ends, in a single step by using ROMP through the utilization of a functionalized ruthenium initiator and a functionalized chain terminator. This strategy affords straightforward and near-quantitative incorporation of the two orthogonal recognition units into a single polymer chain. Self-assembly of the heterotelechelic polymer with monotelechelic polymers bearing complementary hydrogen bonding motifs was achieved by both stepwise and one-pot orthogonal self-assembly strategies. The formation of the targeted supramolecular ABC triblock copolymer was substantiated by using 1-D and 2-D ^{1}H NMR spectroscopy, ITC and viscometry. The ^{1}H NMR spectra of self-assembled polymers and ITC binding isotherms obtained in both the stepwise and one-pot processes revealed that the final, fully self-assembled polymers are identical, independent of the chosen self-assembly routes, suggesting complete specificity and selectivity of each hydrogen bonding interaction with its complementary recognition unit. It is noteworthy that the intermediate telechelic diblock copolymers are useful building blocks for higher order supramolecular polymers with novel architectures.

5.5 Experimental

All reagents were purchased either from Acros Organics, Alfa Aesar, or Sigma-Aldrich and used without further purification unless otherwise noted. CH_2Cl_2 was dried *via* passage through copper oxide and alumina columns. NMR spectra were recorded using a Bruker AV-400 (^{1}H: 400.1 MHz; ^{13}C: 100.6 MHz) spectrometer. Chemical shifts are reported in ppm and referenced to the corresponding residual nuclei in deuterated solvents. 2-D NOESY spectra were recorded using a Bruker AV-500 MHz NMR spectrometer. Mass spectral analyses were provided by the Georgia Tech Mass Spectrometry Facility using a VG-70se spectrometer. Viscosity was measured in dichloromethane using a Cannon semi-micro Ubbelohde viscometer (9722-G59) at 25 °C. Gel-permeation chromatography (GPC) analyses were carried out using a Shimadzu pump coupled to a Shimadzu UV detector with tetrahydrofuran (THF) as the eluant and a flow rate of 1 mL/min on American Polymer Standards column set (100, 1000, 100 000 Å, linear mixed bed). All GPCs were calibrated using poly(styrene) standards and carried out at 25 °C. M_w, M_n, and PDI represent the weight-average molecular weight, number-average molecular weight, and polydispersity index, respectively. Isothermal Titration experiments were carried out on a Microcal VP-ITC isothermal calorimeter using degassed HPLC grade chloroform at 30 °C. The single-site binding constant for a ligand X binding to a polymer was calculated using the thermodynamic parameters obtained from ITC measurements as given by the equation K_a = [unfilled sites]/([filled sites][X]). 6-(4-Vinylphenoxy) hexanoic acid,[8] CA-CT **1**,[8] 7-amido-2-chloro-1,8-naphthyridine **2**,[16] *cis*-docos-11-enedioic acid **3**,[6b] *exo*-norbornene octyl ester **6**,[17] *tert*-butyl ester norbornene

imide **7**,[14] the Hamilton receptor-functionalized ruthenium initiator **9**,[8] and UG **10**[9b] were synthesized according to the previously published procedures.

DAN-CT 5. Diacid **3** (0.20 g, 0.54 mmol) was dissolved in thionly chloride (2 mL) and stirred at 85 °C for 4 h. Excess thionly chloride was removed under reduced pressure to yield the acid chloride which was diluted with dichloromethane (1 mL) and then added dropwise to vigorously stirring concentrated ammonia (25%, 15 mL). The solution was stirred at 25 °C for 24 h, filtered, washed with water, and dried to obtain diamide **4**. To a solution of **2** (0.40 g, 1.3 mmol) and **4** (0.20 g, 0.54 mmol) in 1,4-dioxane (10 mL) were added $Pd(OAc)_2$ (4.9 mg, 0.022 mmol), Xantphos (25 mg, 0.044 mmol), and K_2CO_3 (0.42 g, 3.1 mmol). The mixture was stirred at 100 °C for 24 h and then cooled to rt, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel in dichloromethane/EtOAc (4:1) to yield **5** (0.29 g, 60%). ^{1}H NMR ($CDCl_3$): δ 9.02 (s, 2H), 8.69 (s, 2H), 8.48 (d, J = 8.6 Hz, 4H), 8.10 (d, J = 8.6 Hz, 4H), 5.33 (m, 2H), 2.46 (t, J = 7.6 Hz, 4H), 2.23 (m, 2H), 2.01 (m, 4H), 1.72 (m, 8H), 1.64-1.45 (m, 4H), 1.42-1.28 (m, 32H), 0.94 (m, 6H), 0.84 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 175.6, 172.6, 154.2, 154.0, 153.6, 139.0, 139.0, 130.4, 129.9, 118.3, 113.7, 50.7, 37.9, 32.5, 32.4, 29.7, 29.6, 29.4, 29.3, 29.2, 29.2, 27.1, 26.0, 25.3, 22.7, 13.7, 11.8. HRMS-FAB (m/z): $[M + H]^+$ calcd for $C_{54}H_{81}N_8O_4$, 905.6381; found, 905.6365.

General Polymerization Procedure. The desired amount of monomer **6** (for **PA**) or **7** (for **PB**) was dissolved in anhydrous, degassed CH_2Cl_2 under an argon atmosphere. A solution of initiator **8** (for **PA**) or **9** (for **PB**) in CH_2Cl_2 was added and stirred at 25 °C. Upon complete polymerization, CA-CT **1** (for **PA**) or DAN-CT **5** (for **PB**) was added, stirred at 25 °C for 8 h, and concentrated under reduced pressure. The residue was

purified by repeated precipitation into MeOH or diethyl ether to obtain polymer **PA** or **PB**, respectively.

PC. To a solution of UG **10** (0.12 g, 0.27 mmol) and PEO **11** (0.48 g, 0.23 mmol) in CH_2Cl_2 (15 mL) were added *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (53 mg, 0.28 mmol) and 4-dimethylaminopyridine (5.5 mg, 0.045 mmol). After the mixture was stirred at 25 °C overnight, water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel in dichloromethane/MeOH (10:1) to obtain polymer **PC** (0.48 g, 83%). ^{1}H NMR ($CDCl_3$): δ 12.11 (br s, 1H), 9.52 (br s, 1H), 7.67 (s, 1H), 7.11-6.76 (br, 2H), 5.93 (s, 1H), 5.27 (br, 1H), 5.07 (br, 1H), 4.46-4.25 (m, 3H), 3.89-3.38(m, l × 4H), 3.37 (s, 3H), 3.25 (m, 2H), 2.76-2.37 (m, 4H), 1.59 (s, 3H), 1.52 (m, 2H), 1.38 (s, 3H), 1.27 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H).

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CHAPTER 6

TEMPLATE-ENHANCED RING-OPENING METATHESIS POLYMERIZATION

6.1 Abstract

The template-enhanced ring-opening metathesis polymerization (ROMP) of a pyridine-containing norbornene-based monomer was examined. The poly(norbornene)-based template, functionalized with SCS-Pd(II) pincer complexes that are designed to recognize pyridine substrates with high fidelity, was synthesized *via* ROMP. The template polymerization of the pyridine monomers was attempted under various ROMP conditions.

6.2 Introduction

Templation has been a major research focus in synthetic polymer chemistry because it can provide a harness to control polymer properties such as molecular weight, polydispersity, and sequence.[1] Nature's use of template polymerization to produce biopolymers with controlled lengths, tacticities, and sequences has led polymer chemists to investigate the effects of templates on a variety of polymerization methods including condensation, addition, and chain polymerizations.[1] The most impressive example, based on a fundamental biological process, is nucleic acid templated polymerization to precisely copy the sequence and length of a predefined DNA or RNA strand into a daughter polymer.[2] While this example relates to synthetically templated biopolymers, similar strategies for generating synthetically templated abiotic polymers have recently

emerged in the literature.[3-4] In particular, the template effects on ring-opening metathesis polymerization (ROMP) has been investigated since ROMP is a highly functional group tolerant polymerization technique and therefore well suited for template polymerization.[4]

For example, the group of Luh employed a well-defined poly(norbornene)-based template to study the template effects on the ROMP of norbornene-based monomers (Figure 6.1).[4a] The authors incorporated ferrocene moieties into the side-chains of the single-stranded poly(norbornene) template to increase the solubility as well as to attach the daughter monomers to the template. ROMP of the norbornene-based daughter monomers that are covalently attached to the template afforded an unsymmetrical double-stranded poly(norbornene) under high-dilution conditions, characterized by ^{13}C NMR spectroscopy and scanning tunneling microscopy (STM). After hydrolysis, the isolated daughter polymer exhibited similar molecular weight distribution and degree of polymerization (DP) to those of the template, indicating the formation of a well-defined daughter polymer resulting from the replication of the original polymer template.

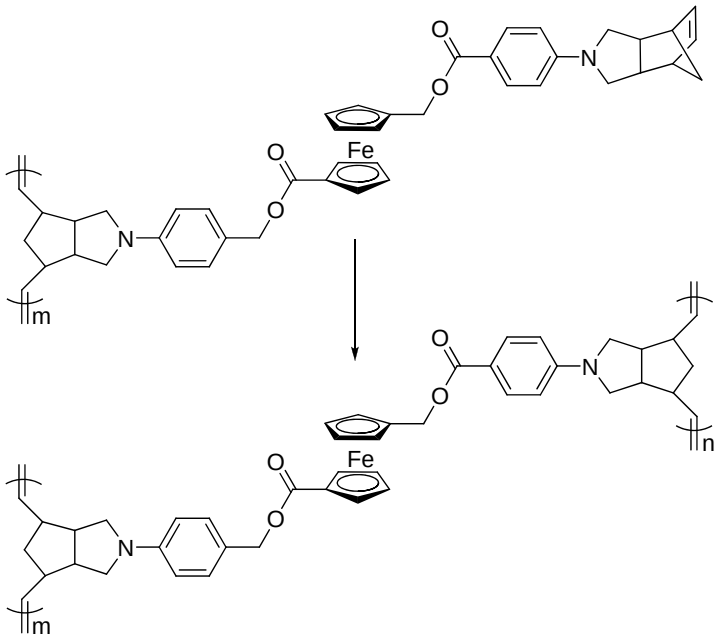


Figure 6.1. Templated polymerization of covalently attached norborene-based monomers.

Another example of ROMP-based template polymerization was reported by Weck and co-workers, who utilized hydrogen bonding to self-assemble daughter monomers into a polymer template (Figure 6.2).[4b] The diamidopyridine-functionalized poly(norbornene)-based template is designed to recognize thymine substrates and was synthesized *via* ROMP. The resulting template was used to enhance the ROMP of the thymine-functionalized daughter monomers producing a bis-poly(norbornene) complex. In addition, a solid-supported diamidopyridine template was used to extract the daughter polymer from the support after the template polymerization. This study demonstrated that the polymeric template can enhance both the rate of the polymerization by inducing an increase in local monomer concentration and can be used to control the resulting polymerization.

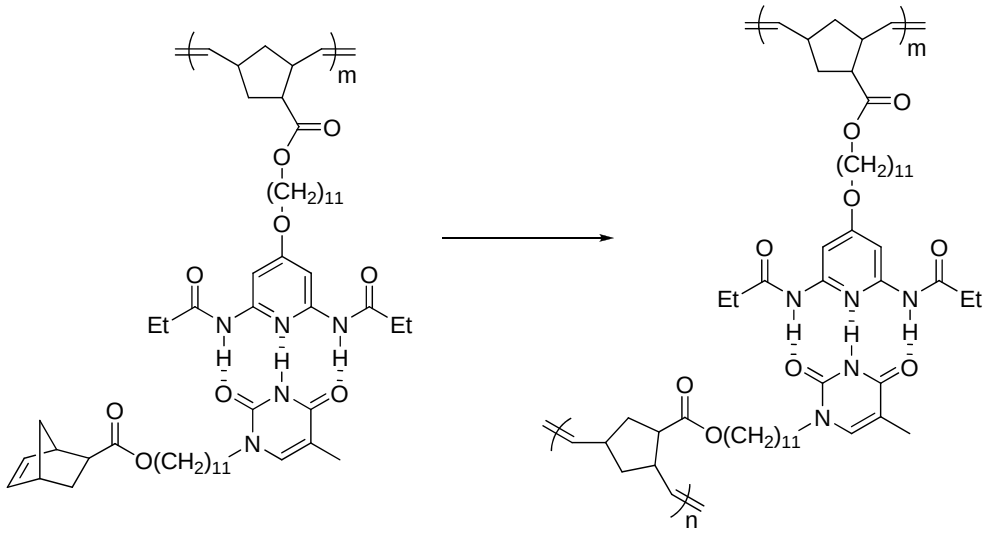


Figure 6.2. Hydrogen bonding-based templated polymerization.

The two examples, however, are not perfect systems for template polymerizations. The first example utilized covalent linkages between a template and daughter monomers, resulting in difficulties separating the daughter polymer from the template. Moreover, hydrolysis to extract the daughter polymer did not produce the original polymer template, indicating the limited recycling of the template. While highly desirable for separating the daughter polymer, the second system based on noncovalent interactions can be problematic in some cases. In particular, since the template polymerization requires very low concentration and/or polar solvents, the hydrogen bonding between diaminopyridine and thymine might not be strong enough to hold template:monomer complexes together under the conditions. To address these limitations, metal coordination between SCS-Pd(II) pincer complexes and pyridines is investigated in this chapter because of its high association constant and reversibility. The design involves the use of a SCS-Pd(II) pincer-based poly(norbornene) template that recognizes pyridine-containing norbornene

monomers, followed by the template polymerization of the resulting complex *via* ROMP (Figure 6.3).

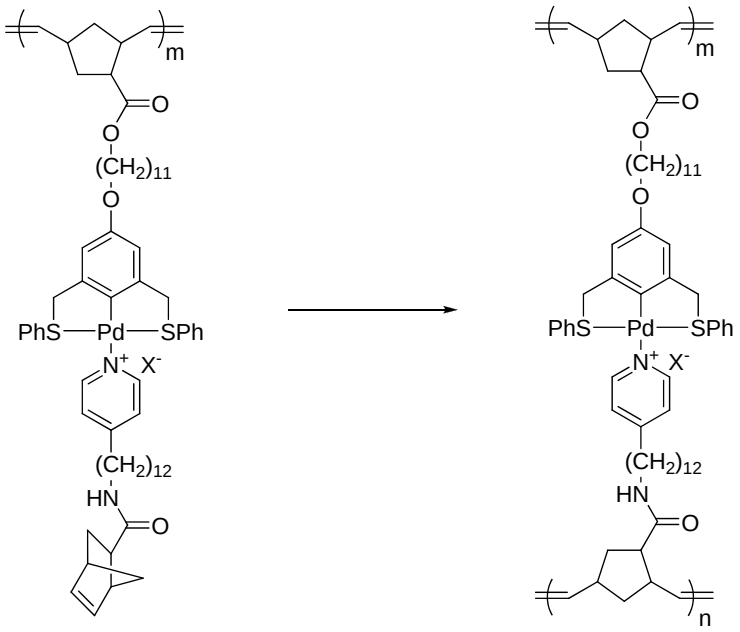


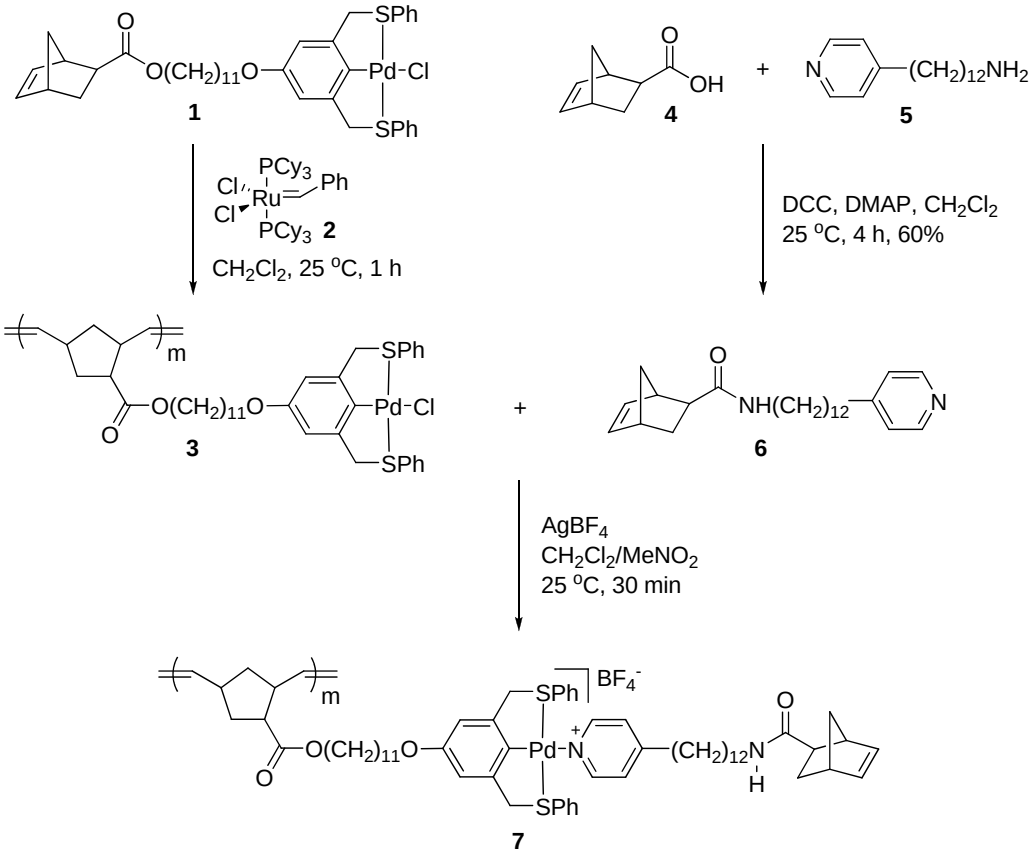
Figure 6.3. Metal coordination-based templated polymerization.

6.3 Results and Discussion

A SCS-Pd(II) pincer complex-containing template **3** was synthesized by ROMP of monomer **1** with 5 mol% of Grubbs' first-generation initiator **2** in dichloromethane.[5] The molecular weight and polydispersity of **3** were determined by gel-permeation chromatography (GPC) (M_n = 13 000, PDI = 1.25). Pyridine-containing monomer **6** was synthesized by the *N*,*N*'-dicyclohexylcarbodiimide-mediated esterification of *exo*-norbornene acid **4** with **5**. Metal coordination between **3** and **6** was carried out in the presence of $AgBF_4$ to obtain a template:monomer complex **7**. The synthetic pathway is outlined in Scheme 6.1. To investigate the metal coordination-based template effects on

the ROMP, the templated polymerization of **7** was attempted under various ROMP conditions, *i.e.* Grubbs' first- or third-generation initiator, dichloromethane, dichloroethane, or chloroform as a solvent, and 0.5, 1, or 10 mM concentration. In all cases, however, both the disappearance of the olefinic proton resonance originating from **7** at 6.12 ppm and the increase of the olefinic signal corresponding to the desired polymer at 5.28 ppm were not observed in the ^{1}H NMR spectra, indicating that the desired product did not form under the reaction conditions. It is likely that no reactivity in the ROMP of **7** is due to undesired interactions between the template:monomer complex and the initiator. The exact reason for this, however, is not yet fully understood.

Scheme 6.1. Synthesis of template:monomer complex *via* metal coordination.



In order to circumvent the problems in the metal coordination-based systems, an alternative strategy based on quadruple hydrogen bonding between ureidoguanosine (UG) and diamidonaphthyridine (DAN) was designed (Figure 6.4). The synthesis of UG-containing templates and DAN-functionalized monomers is currently underway and the subsequent templated polymerization will be investigated

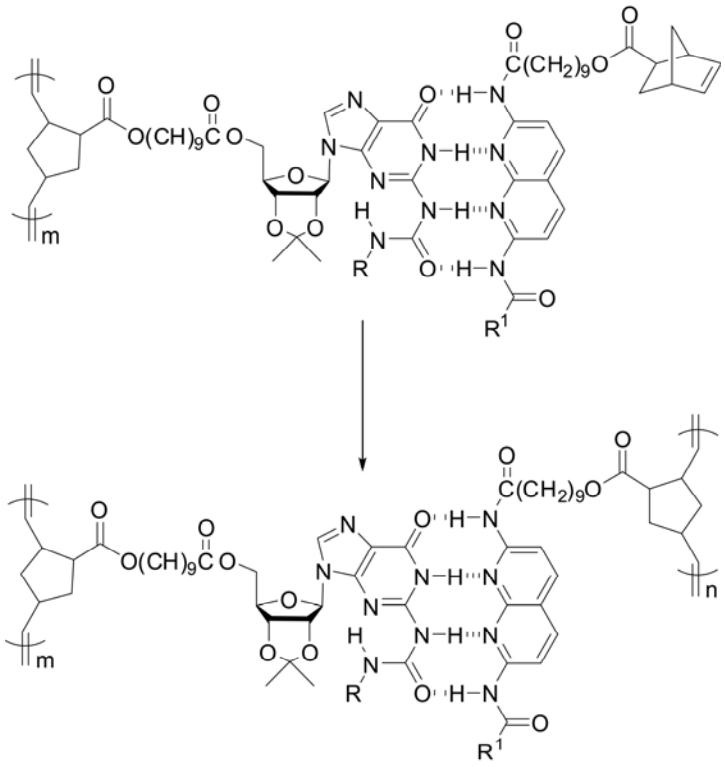


Figure 6.4. Quadruple hydrogen bonding-based templated polymerization.

6.4 Conclusion

The metal coordination-based template effects on the ROMP of a pyridine-containing monomer were examined. A SCS-Pd(II) pincer-functionalized template was synthesized by ROMP and then self-assembled with pyridine monomers *via* metal coordination. The templated polymerization of the resulting template:monomer complex was attempted under a variety of ROMP conditions. Unfortunately, no polymerization of the complexed monomer was observed. An alternative that utilizes quadruple hydrogen bonding has been introduced and the templated polymerization will be investigated.

6.5 Experimental

All reagents were purchased either from Acros Organics, Alfa Aesar, or Sigma-Aldrich and used without further purification unless otherwise noted. CH_2Cl_2 was dried *via* passage through copper oxide and alumina columns. NMR spectra were recorded using a Bruker AV-400 (^{1}H: 400.1 MHz; ^{13}C: 100.6 MHz) spectrometer. Chemical shifts are reported in ppm and referenced to the corresponding residual nuclei in deuterated solvents. Gel-permeation chromatography (GPC) analyses were carried out using a Shimadzu pump coupled to a Shimadzu UV detector with tetrahydrofuran (THF) as the eluant and a flow rate of 1 mL/min on American Polymer Standards column set (100, 1000, 100 000 Å, linear mixed bed). All GPCs were calibrated using poly(styrene) standards and carried out at 25 °C. M_w, M_n, and PDI represent the weight-average molecular weight, number-average molecular weight, and polydispersity index, respectively. Monomer **1**,[5] *exo*-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid **4**,[6] and 12-

pyridin-4-yldodecylamine **5**[7] were synthesized according to the previously published procedures.

Template 3. Monomer **1** (0.25 g, 0.32 mmol) was dissolved in anhydrous, degassed CH_2Cl_2 (20 mL) under an argon atmosphere. A solution of initiator **2** (13 mg, 0.016 mmol) in CH_2Cl_2 was added and stirred at 25 °C. Upon complete polymerization, ethyl vinyl ether was added to quench the polymerization. The residue was purified by repeated precipitation into MeOH to obtain polymer **3**. ^{1}H NMR ($CDCl_3$): δ 7.78 (m, 4H), 7.32 (m, 6H), 6.55 (s, 2H), 5.50-5.17 (br, 2H), 4.58 (br, 4H), 4.03 (m, 2H), 3.82 (m, 2H), 3.24-2.30 (br, 3H), 2.03-1.50 (br, 8H), 1.98-1.07 (m, 14H). ^{13}C NMR ($CDCl_3$): δ 174.4, 156.8, 151.3, 149.9, 132.3, 131.2, 129.6, 129.5, 108.7, 108.6, 67.9, 64.2, 51.5, 48.0, 45.4, 40.4, 37.3, 36.0, 29.3, 29.2, 28.9, 28.6, 26.0, 25.8. GPC: M_w = 16.0 kDa, M_n = 13.0 kDa, and PDI = 1.25.

Monomer 6. To a solution of **4** (0.20 g, 1.5 mmol) and **5** (0.57 g, 2.2 mmol) in CH_2Cl_2 (10 mL) were added *N,N'*-dicyclohexylcarbodiimide (0.36 mg, 1.7 mmol) and 4-dimethylaminopyridine (8.8 mg, 0.072 mmol). After the mixture was stirred at 25 °C for 4 h, water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel in hexanes/EtOAc (2:3) to obtain polymer **6** (0.33 g, 60%). ^{1}H NMR ($CDCl_3$): δ 8.48 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 6.12 (m, 2H), 5.52 (br, 1H), 3.23 (m, 2H), 2.91 (br, 2H), 2.58 (t, J = 7.6 Hz, 2H), 1.95 (m, 2H), 1.74 (m, 2H), 1.62 (m, 2H), 1.49 (m, 2H), 1.36-1.21 (m, 17H). ^{13}C NMR ($CDCl_3$): δ 175.5, 151.8,

149.6, 138.3, 136.0, 123.9, 47.2, 46.4, 44.8, 41.6, 39.6, 35.2, 30.5, 30.3, 29.8, 29.6, 29.5, 29.5, 29.5, 29.4, 29.3, 29.2, 26.9.

Template:monomer complex 7. To a solution of **3** (55 mg, 0.071 mmol) and **6** (27 mg, 0.071 mmol) in CH_2Cl_2 (4 mL) was added $AgBF_4$ (15 mg, 0.077 mmol) in $MeNO_2$ (1 mL). After stirring at 25 °C for 30 min, the precipitated AgCl(s) was removed by centrifugation. The supernatant liquid was filtered through a plug of Celite and subsequently through a 0.2 μm syringe filter. The solvent was removed *in vacuo* to yield the complex **7**. ^{1}H NMR (CD_2Cl_2): δ 7.88 (br, 2H), 7.62 (m, 4H), 7.38 (m, 6H), 7.04 (br, 2H), 6.68 (s, 2H), 6.12 (br, 2H), 5.75 (br, 1H), 5.46-5.16 (br, 2H), 4.73 (br, 4H), 4.10-3.82 (m, 4H), 3.21-2.43 (m, 9H), 2.08-1.07 (m, 47H).

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CHAPTER 7

CONCLUSIONS AND FUTURE DIRECTIONS

7.1 Abstract

This chapter summarizes the conclusions of the research results presented in this thesis. The main contributions of this thesis to current functionalization methods in polymeric materials are reviewed. The advantages and limitations of each strategy developed in this thesis are also included. Finally, a potential view of new projects that might result from the orthogonal functionalization strategies developed herein is presented.

7.2 Introduction

In polymer science, highly efficient and selective functionalization of macromolecular architectures has remained a major challenge for several decades since typical functionalization approaches rely on traditional covalent reactions that are often cumbersome, time-consuming, and not quantitative. Nature's multifunctionalization strategy for creating vast libraries of biological materials with a high degree of complexity has been an inspiration to address this challenge. This thesis primarily aims to develop efficient and orthogonal functionalization strategies by introducing click reactions and noncovalent interactions within polymeric materials. This goal was achieved by the research presented in this thesis. Specifically, orthogonal and high-yielding polymer functionalization strategies were developed using click reactions. Furthermore, easy and efficient strategies for the synthesis of supramolecular telechelic

polymers were developed, and noncovalent interactions such as hydrogen bonding and metal coordination were used to form supramolecular block copolymers.

7.3 Summary and Conclusions

Chapter 2 presents results of our efforts on the functionalization of side-chain functionalized polymers using two different click reactions. Poly(norbornene)-based random copolymers bearing an azide along with either an aldehyde or ketone functionality on each repeating unit were synthesized *via* ROMP. The orthogonal functionalization of the resulting copolymers was investigated using 1,3-dipolar cycloaddition and hydrazone formation. While the azide- and aldehyde-containing copolymers were insoluble, the azide- and ketone-functionalized copolymers were fully soluble in common organic solvents and could be quantitatively functionalized with a library of small organic and biological molecules in both stepwise and one-pot fashions. NMR and IR spectroscopies proved that all functionalization transformations proceeded quantitatively in an orthogonal manner with high fidelity and absolute selectivity under mild reaction conditions. The results of this study were very promising due to the combination of control over polymer properties such as molecular weight and polydispersity, functional group tolerance, and modular multifunctionalization in quantitative yields, which have not been fully achieved by previous systems reported in the literature.[1]

Another advancement of our covalent functionalization strategy is presented in Chapter 3. The synthesis of highly functionalized terpolymers is desirable for the application in drug delivery systems because a number of drug molecules, targeting

moieties, and solubilizing groups can be attached to polymer backbones. Poly(norbornene)-based random terpolymers possessing azide, ketone, and maleimide functionalities along side-chains were synthesized using ROMP. Subsequent side-chain functionalizations were achieved in an orthogonal and stepwise fashion by using maleimide-thiol coupling, 1,3-dipolar cycloaddition, and hydrazone formation. The combination of the three different transformations allowed for the fast and precise site-specific functionalization of terpolymers, demonstrating their potential use in drug delivery.[2]

Chapter 4 presents results of an extensive study on main-chain functionalization to obtain supramolecular multiblock copolymers using noncovalent interactions. Supramolecular multiblock copolymers are of significant interest since unprecedented polymeric blends with tunable physical properties can be obtained easily by mixing two symmetrically end-functionalized polymers.[3] In this chapter, a new bimetallic ruthenium initiator was synthesized and used to polymerize norbornene-based monomers, affording polymers that are living at both chain-ends, with full control over molecular weight and polydispersity. SCS-Pd(II) pincer- and pyridine-functionalized symmetrical telechelic polymers were synthesized in a single step *via* ROMP using the bis-ruthenium initiator, followed by termination with functional chain-terminators. Self-assembly of the resulting telechelic polymers was achieved by metal coordination between the corresponding recognition units in the presence of $AgBF_4$, resulting in the formation of supramolecular multiblock copolymers. This study also demonstrated that the bulk polymer properties can be tuned by the controlled addition of the activating agent $AgBF_4$.[4]

Chapter 5 presents another advancement of the noncovalent functionalization strategy for the synthesis of supramolecular ABC triblock copolymers that have not been explored although these are promising candidates for new materials with unprecedented properties. The synthesis of a heterotelechelic polymer displaying two different recognition moieties as the central block, however, is non-trivial. Using ROMP, the end groups of polymers can be controlled by use of a functionalized ruthenium initiator and a functionalized chain-terminator.[5] To incorporate reversible, noncovalent interactions between individual components of multiblock copolymers, a dual-telechelic polymer was synthesized in a single step in this manner. Fully self-assembled ABC triblock copolymers were obtained by two orthogonal hydrogen bonding interactions between this polymer and complementary monotelechelic polymers in both stepwise and one-pot fashions. It is noteworthy that the incorporation of side-chain functionalities in these polymers further increases the level of structural complexity.[6]

Chapter 6 presents our attempts at the template-assisted polymer synthesis using noncovalent interactions. Our initial interest lied in examining the metal coordination-based template effects on the ROMP of a pyridine-containing norbornene-based monomer. A SCS-Pd(II) pincer-functionalized polymer was employed as a template for the self-assembly of pyridine monomers through metal coordination. The templated polymerization of the resulting template:monomer complex, however, was not successful. The lesson learnd from this study was the incompatibility of ROMP with the palladated pincer-pyridine complex, which led us to seek an alternative to the metal coordination-based system. The templated polymerization based on quadruple hydrogen bonding between UG and DAN is now underway.

7.4 Potential Future Directions

Since the work presented in this thesis has the potential to overcome some of the drawbacks associated with traditional covalent approaches to synthesize multifunctional polymers, continuing advances in this area are expected. This section will suggest potential future work designed to expand upon the orthogonal functionalization strategies developed in this thesis.

7.4.1 Drug Delivery Vehicles Based on Terpolymers

A unique application of highly functionalized copolymers is drug delivery systems where small drug molecules can be attached to a well-defined multivalent polymeric carrier. The drug-polymer conjugates have been widely investigated since the development of monoclonal antibodies by Milstein and Köhler, and Ringsdorf's model for drug delivery systems based on synthetic polymers in the 1970s.[7-9] In Ringsdorf's model, a number of drug molecules are bound to a polymer backbone through a biodegradable linker molecule which allows for the release of the drugs at the site of interest.[7,9] In addition, the drug-polymer conjugates can contain targeting moieties such as peptides, antibodies, or sugars as well as solubilizing groups such as poly(ethylene glycol) (PEG). The macromolecular carrier should be water-soluble and nontoxic, as well as exhibit suitable functional groups for the quantitative and selective attachments of the desired molecules. According to this model, our terpolymer system presented in Chapter 3 is well suited for the preparation of drug-polymer conjugates for several reasons: (i) the well-defined poly(norbornene) backbone and three different side-chain functionalities are biocompatible, (ii) the drugs, targeting moieties, and solubilizing groups can be quantitatively and orthogonally attached to the backbone using three diffent

transformations such as 1,3-dipolar cycloaddition, hydrazone formation, and maleimide-thiol coupling, and (iii) acid-cleavable hydrazone linkages offer drug release by pH drop in endosomal compartment.[10]

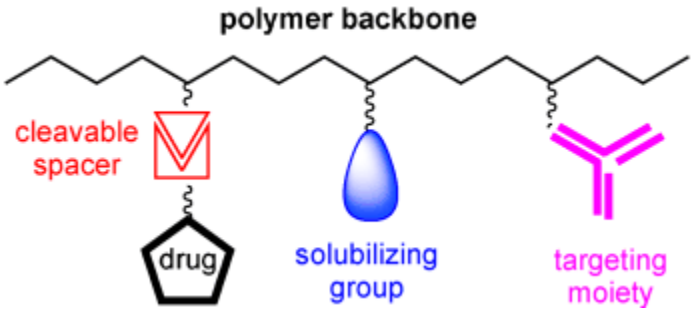

Figure 7.1. Ringsdorf's model for drug delivery ststems based on synthetic polymers (Adapted image).[7,9]

7.4.2 Side-Chain Functionalized Supramolecular ABC Triblock Copolymers

Another potential extension of the orthogonal functionalization strategies presented in this thesis is a combination of main-chain self-assembly using noncovalent interaction and side-chain functionalization using click reactions to construct more complex materials for a variety of applications in drug delivery, molecular machines, and electronic devices. A specific example, based on a combination of the supramolecular ABC triblock copolymer and covalently functionalized terpolymer presented in chapters 5 and 3, respectively, is outlined in Figure 7.2.[2,6] In this system, three different homopolymers possessing either azide, ketone, or maleimide functionalities on each side-chain can be functionalized *via* 1,3-dipolar cycloaddition, hydrazone formation, and maleimide-thiol coupling, respectively, followed by main-chain self-assembly between

the individual blocks using two orthogonal hydrogen bonding interactions, the Hamilton receptor-cyanuric acid and UG-DAN, to obtain a fully side-chain functionalized supramolecular ABC triblock cpolymer. Such use of coupled covalent and noncovalent functionalization approaches can be useful for creating materials with unique tunable properties.

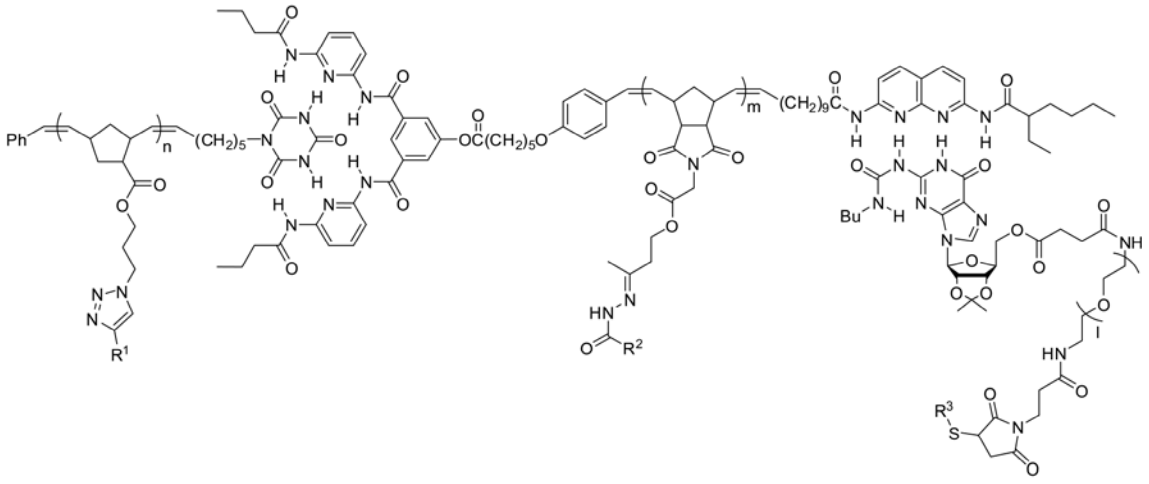

Figure 7.2. Side-chain functionalized supramolecular ABC triblock copolymer.

7.4.3 Orthogonal Polymerizations *via* Bifunctional Initiators

A methodology for the synthesis of functionalized ruthenium initiators was developed by carbene exchange of Grubbs' first-generation initiator.[4-6] In Chapter 5, a Hamilton receptor-functionalized ruthenium initiator was synthesized and used to polymerize norbornene-based monomers to obtain suprarmolecular heterotelechelic polymers in a single step.[5] There are numerous possibilities for future work dealing with functionalized ruthenium initiators. An example is a bifunctional ruthenium initiator that

can be prepared by incorporating another initiating moiety onto a ruthenium initiator, allowing for the synthesis of block copolymers. Specifically, a hydroxy-functionalized ruthenium initiator can be prepared by this method and used to produce poly(lactic acid) (PLA)-*block*-poly(norbornene) (PNB) copolymers by combining the hydroxy-initiated ring-opening polymerization (ROP) of lactides with the ruthenium-initiated ROMP of norbornenes in a single step (Figure 7.3). This scenario might be possible based on the work of the Hedrick and Waymouth groups, in which ROP of lactide is achieved with 1,5,7-triazabicyclo-[4,4,0]-dec-5-ene (TBD) as a catalyst at room temperature in CH_2Cl_2.[11] These reaction conditions can be also used for the ROMP of norbornenes suggesting orthogonality of both polymerization techniques. This bifunctional ruthenium initiator-based orthogonal polymerization strategy will open a new pathway towards easy and rapid synthesis of PLA-*b*-PNB copolymers useful in the field of tissue engineering.[12]

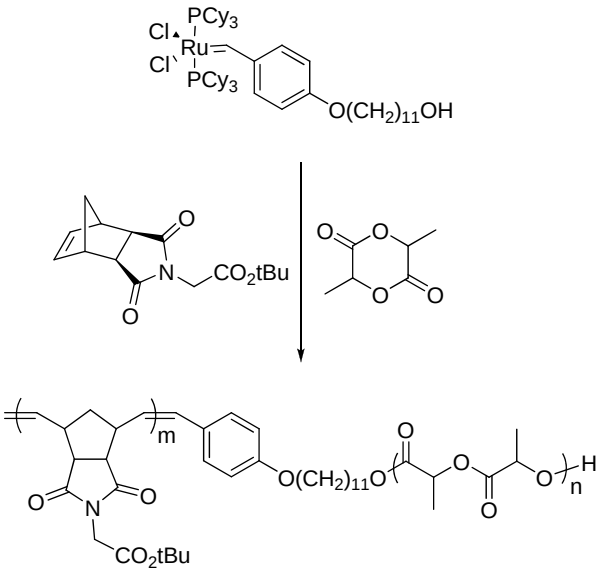

Figure 7.3. Orthogonal polymerizations *via* a hydroxyl-functionalized ruthenium initiator towards PLA-*b*-PNB copolymers.

7.5 Conclusion

This thesis has demonstrated several unique examples of efficient and orthogonal polymer functionalization that rely on either covalent or noncovalent approaches. The work presented in this thesis, as a whole, has the potential to address some of the key problems of traditional covalent polymer synthetic strategies by introducing click chemistry and supramolecular interactions within polymeric systems. Continuing advances in this area will further improve the versatility and applicability of the orthogonal functionalization strategies developed herein, thereby fulfilling the ultimate goal of mimicking the complexity of nature.

7.6 References

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APPENDIX A

SUPPLEMENTAL INFORMATION FOR CHAPTER 2

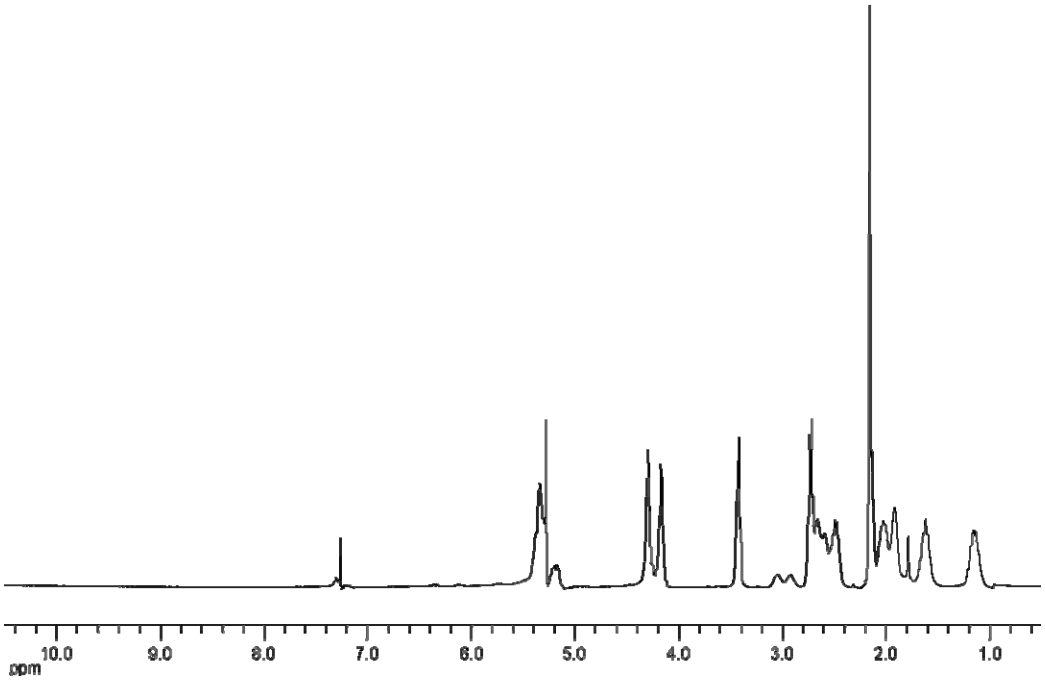

Figure A.1. ^{1}H NMR spectrum of polymer **15** in $CDCl_3$.

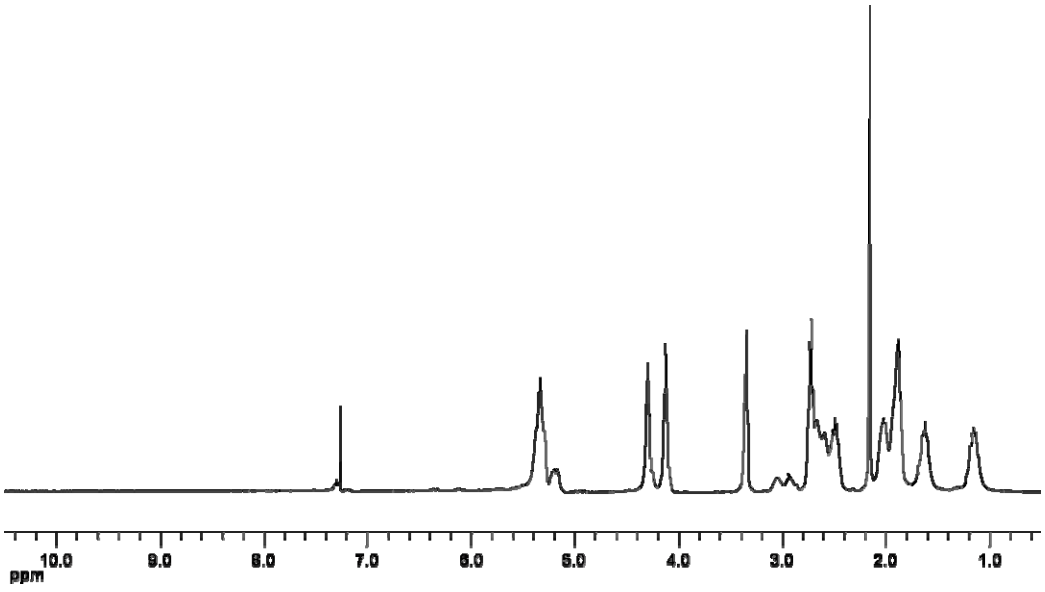

Figure A.2. ^{1}H NMR spectrum of polymer **16** in $CDCl_3$.

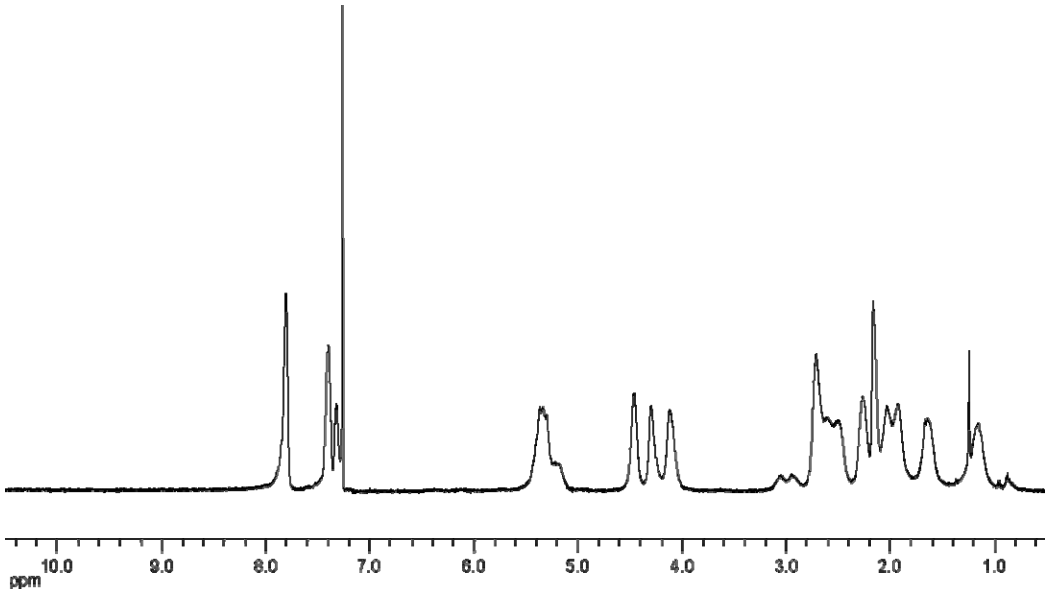

Figure A.3. ^{1}H NMR spectrum of polymer **17a** in $CDCl_3$.

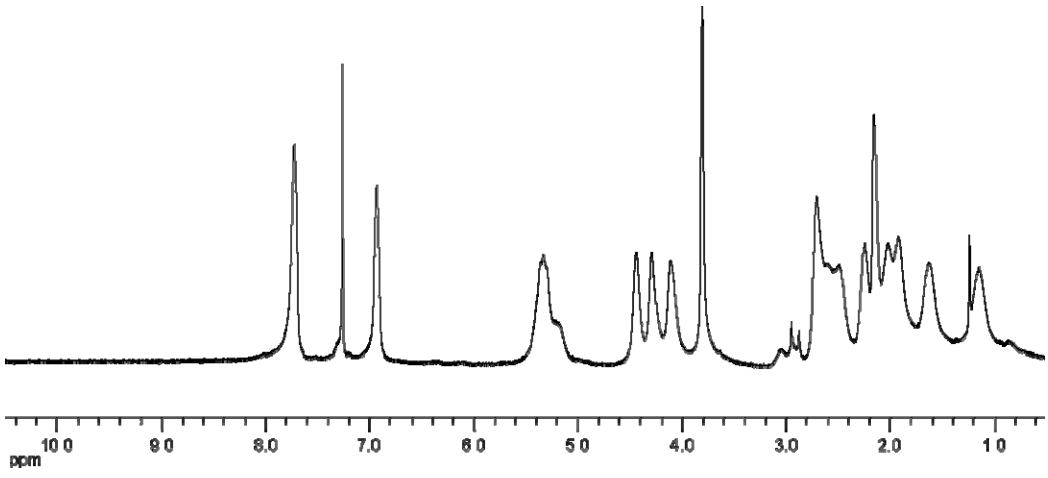

Figure A.4. ^{1}H NMR spectrum of polymer **17b** in $CDCl_3$.

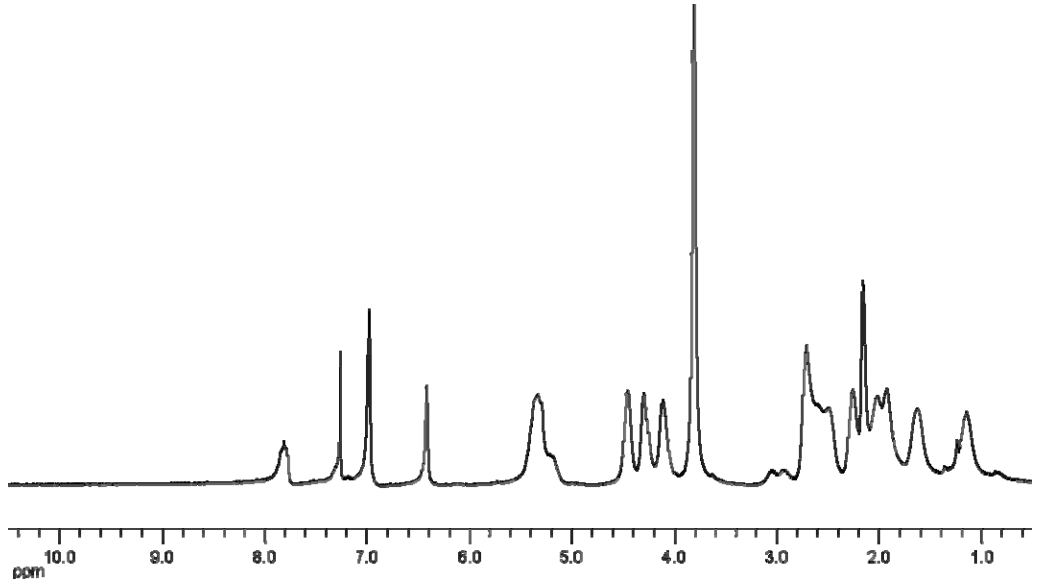

Figure A.5. ^{1}H NMR spectrum of polymer **17c** in $CDCl_3$.

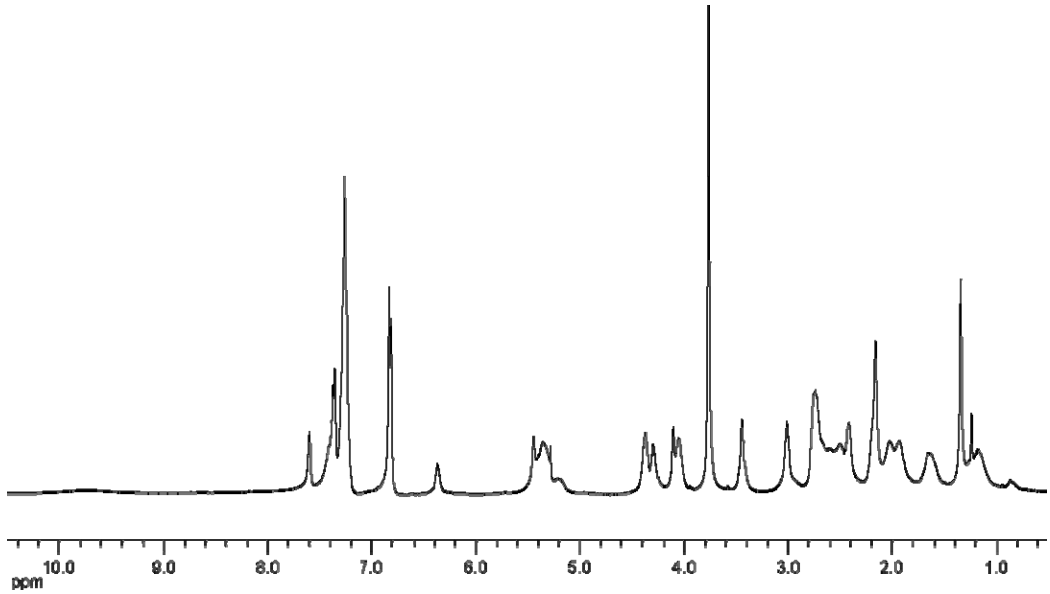

Figure A.6. ^{1}H NMR spectrum of polymer **17d** in $CDCl_3$.

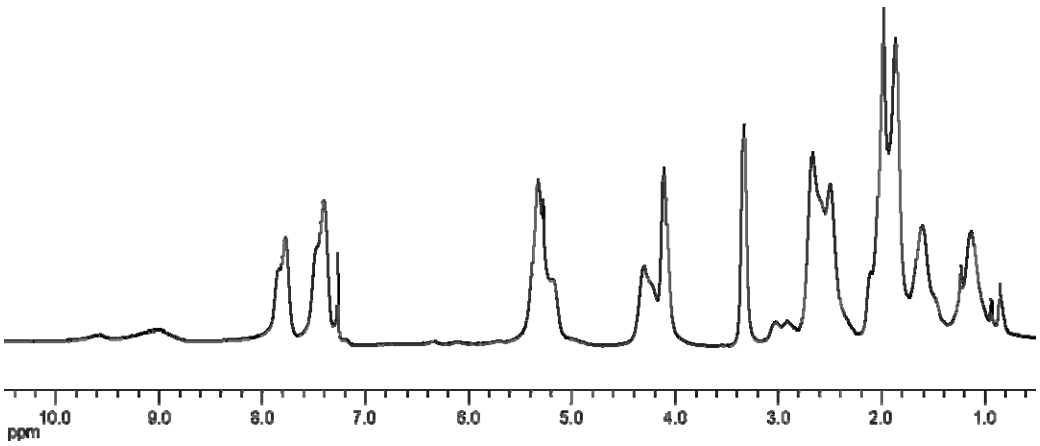

Figure A.7. ^{1}H NMR spectrum of polymer **18a** in $CDCl_3$.

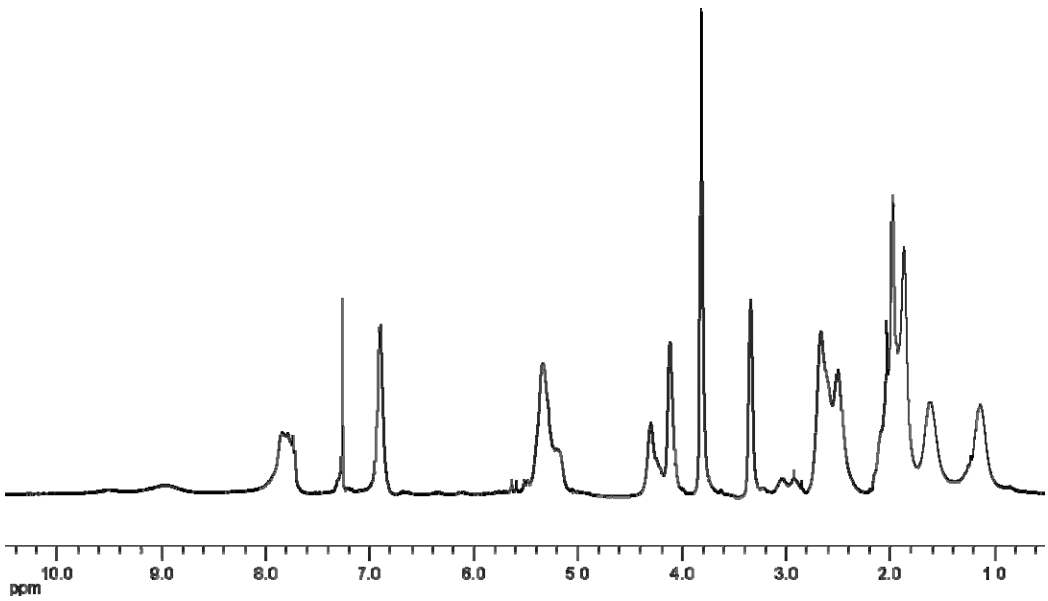

Figure A.8. ^{1}H NMR spectrum of polymer **18b** in $CDCl_3$.

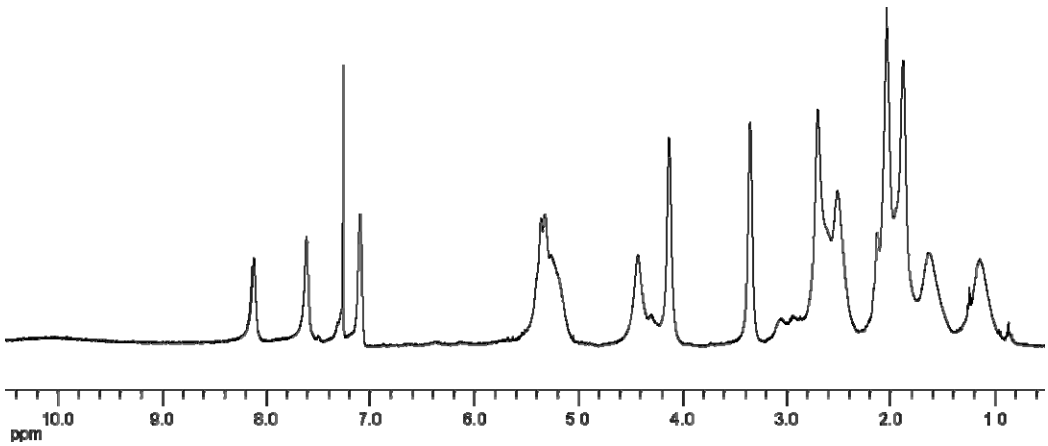

Figure A.9. ^{1}H NMR spectrum of polymer **18c** in $CDCl_3$.

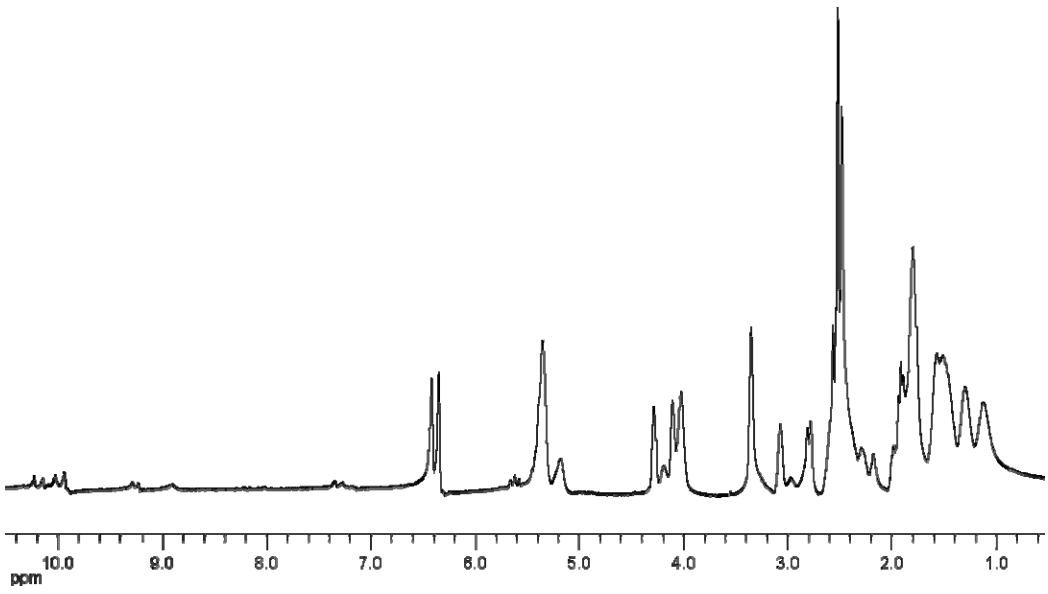

Figure A.10. ^{1}H NMR spectrum of polymer **18d** in DMSO-d_6.

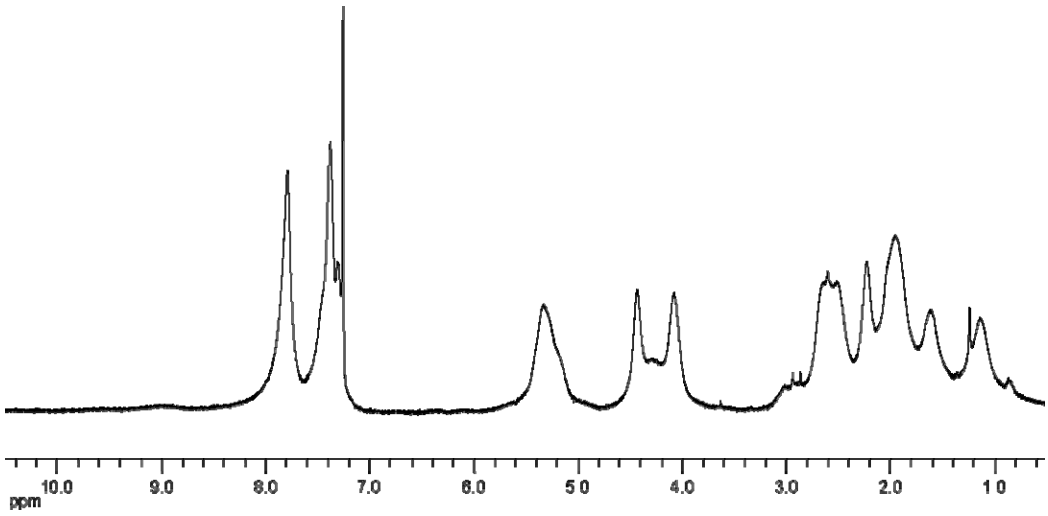

Figure A.11. ^{1}H NMR spectrum of polymer **19a** in $CDCl_3$.

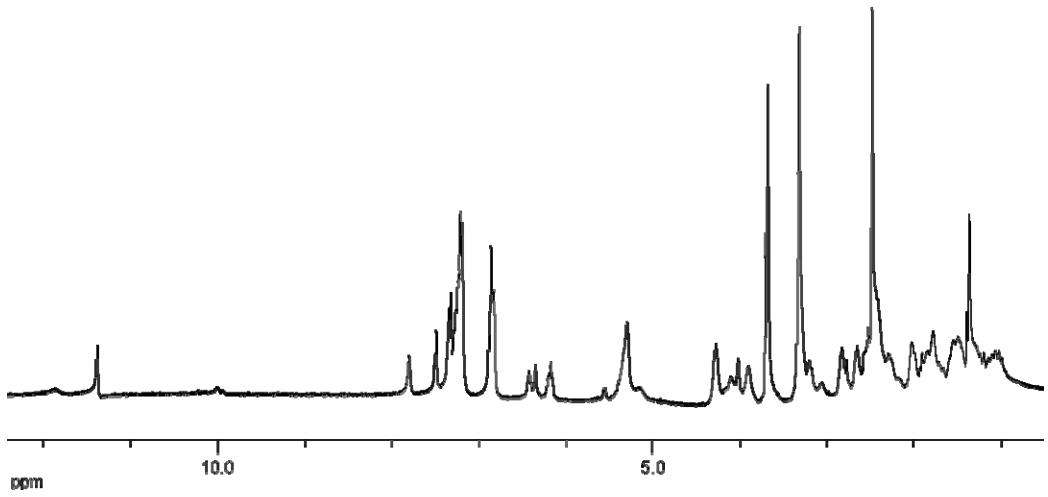

Figure A.12. ^{1}H NMR spectrum of polymer **19b** in DMSO-d_6.

APPENDIX B

SUPPLEMENTAL INFORMATION FOR CHAPTER 4

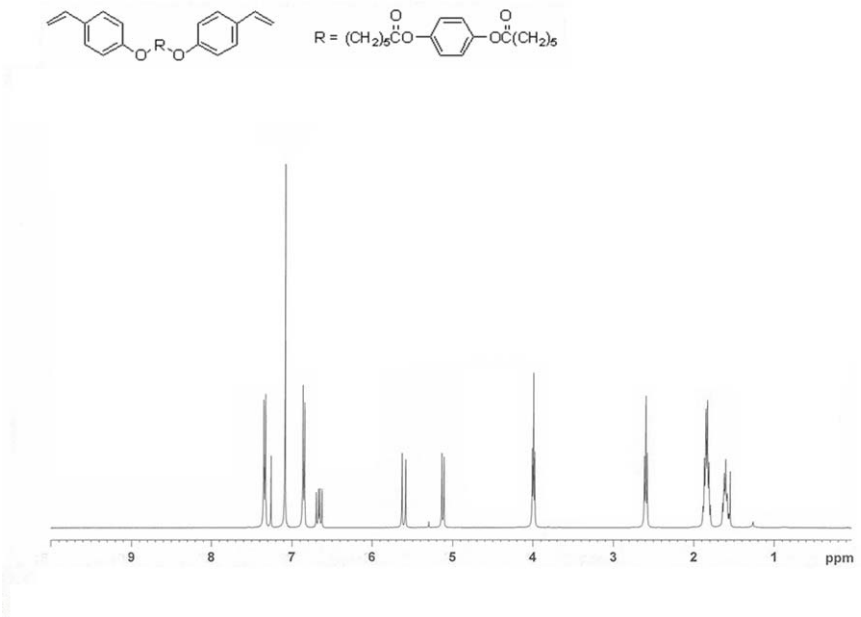

Figure B.1. ^{1}H NMR spectrum of bis-styrene **2** in $CDCl_3$.

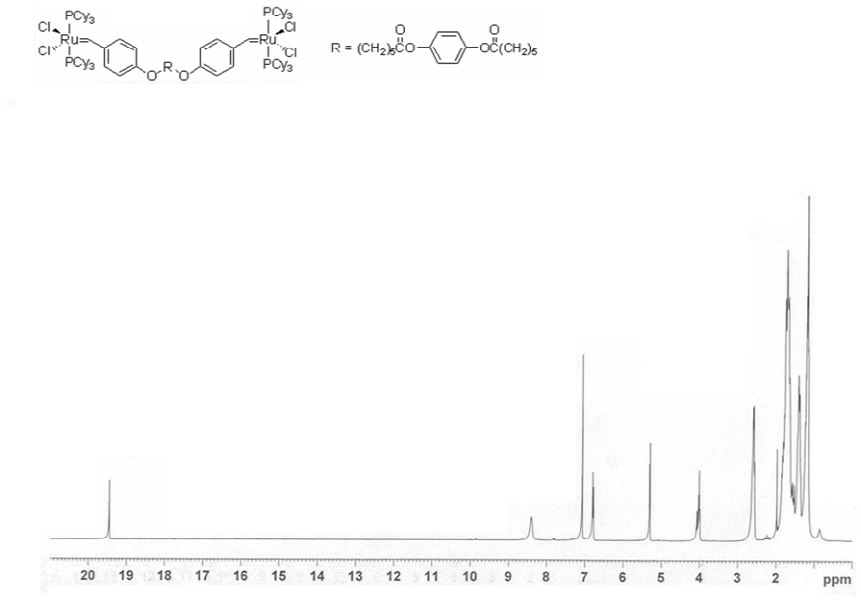

Figure B.2. ^{1}H NMR spectrum of bis-ruthenium initiator **4** in CD_2Cl_2.

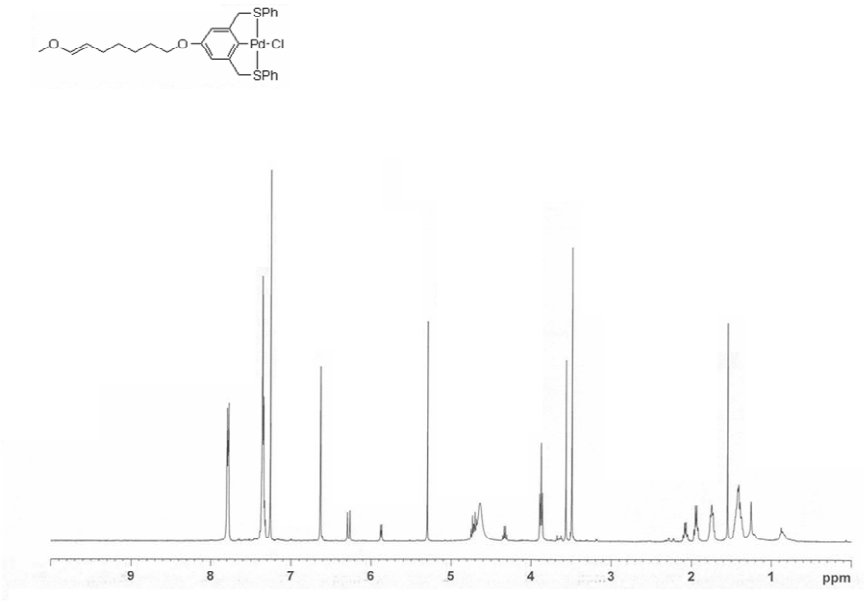

Figure B.3. ^{1}H NMR spectrum of CT **8** in $CDCl_3$.

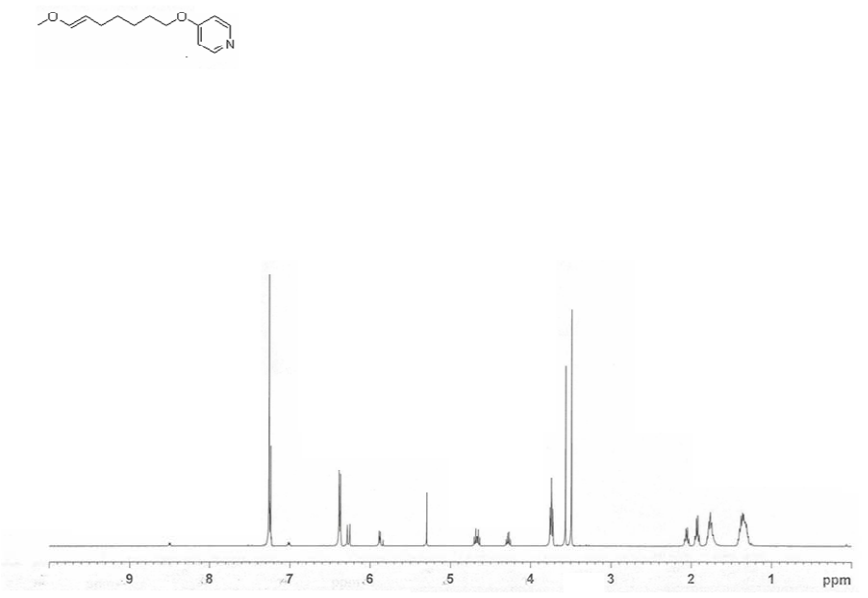

Figure B.4. ^{1}H NMR spectrum of CT **9** in $CDCl_3$.

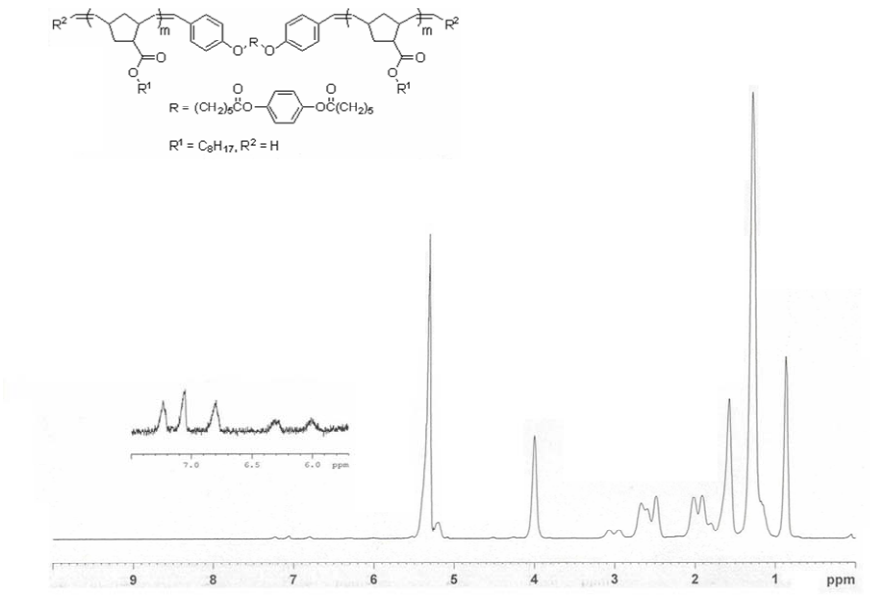

Figure B.5. ^{1}H NMR spectrum of polymer **12** in CD_2Cl_2.

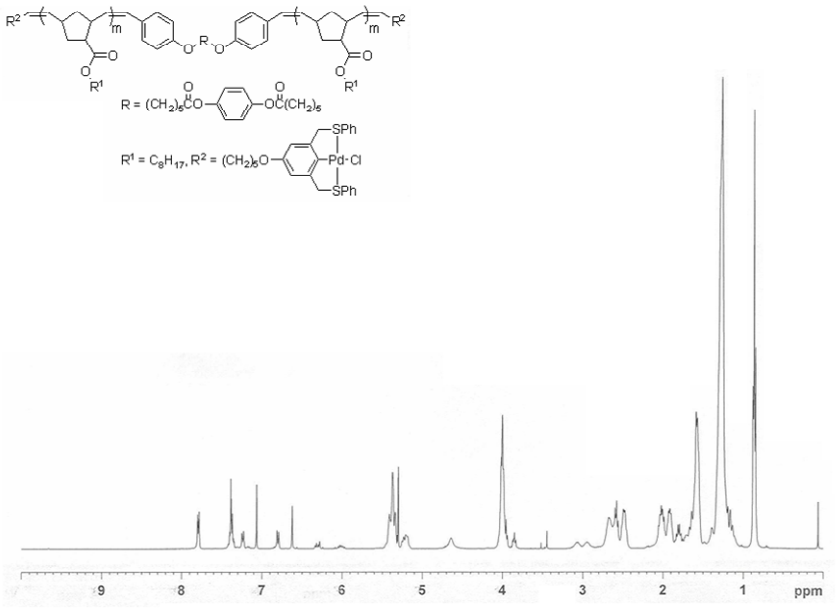

Figure B.6. ^{1}H NMR spectrum of polymer **13** in CD_2Cl_2.

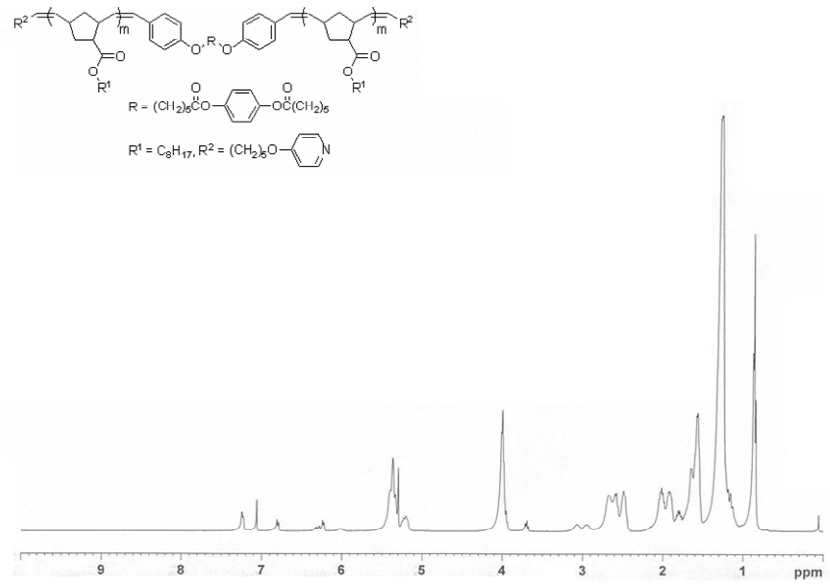

Figure B.7. ^{1}H NMR spectrum of polymer **14** in CD_2Cl_2.

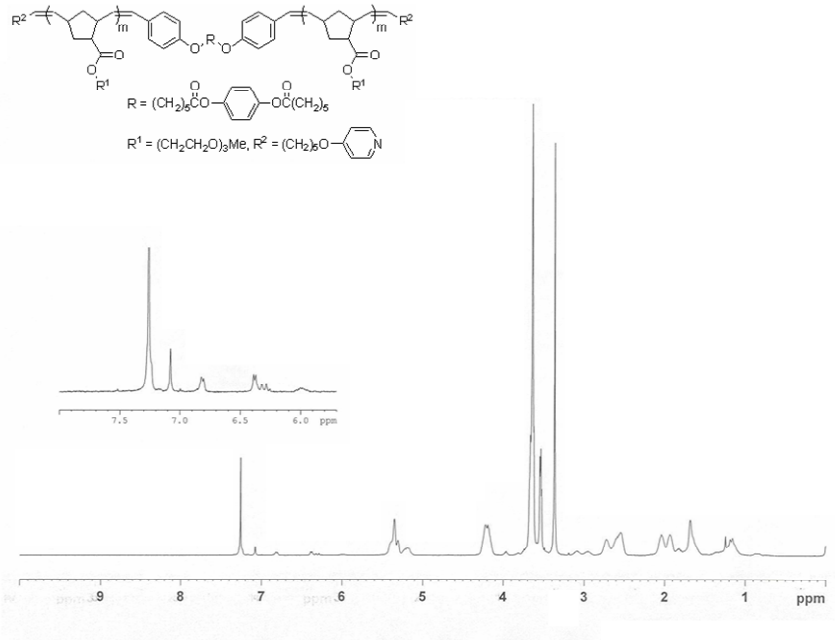

Figure B.8. ^{1}H NMR spectrum of polymer **15** in CD_2Cl_2.

APPENDIX C

SUPPLEMENTAL INFORMATION FOR CHAPTER 5

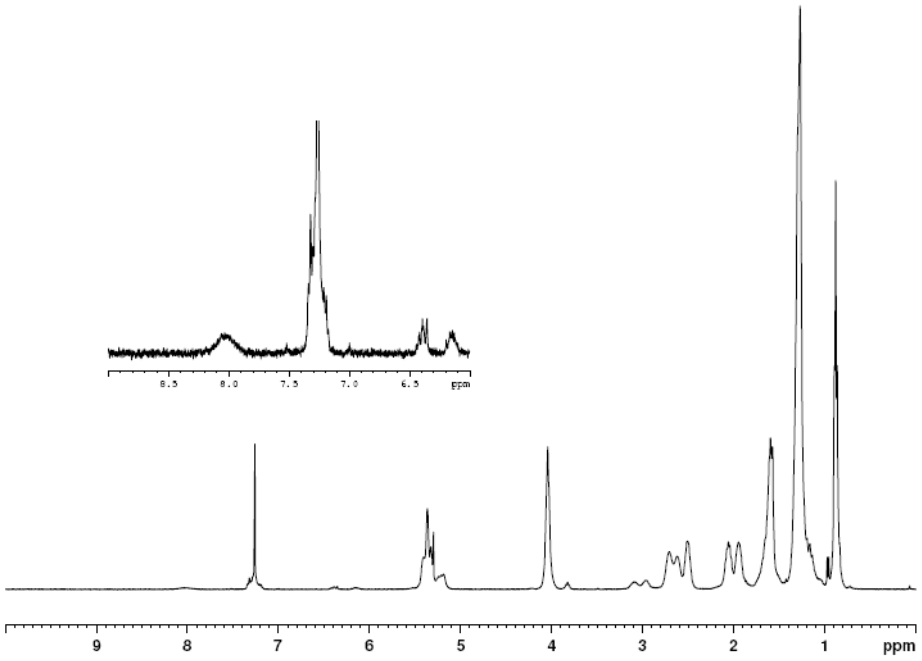

Figure C.1. ^{1}H NMR spectrum of **PA** in $CDCl_3$.

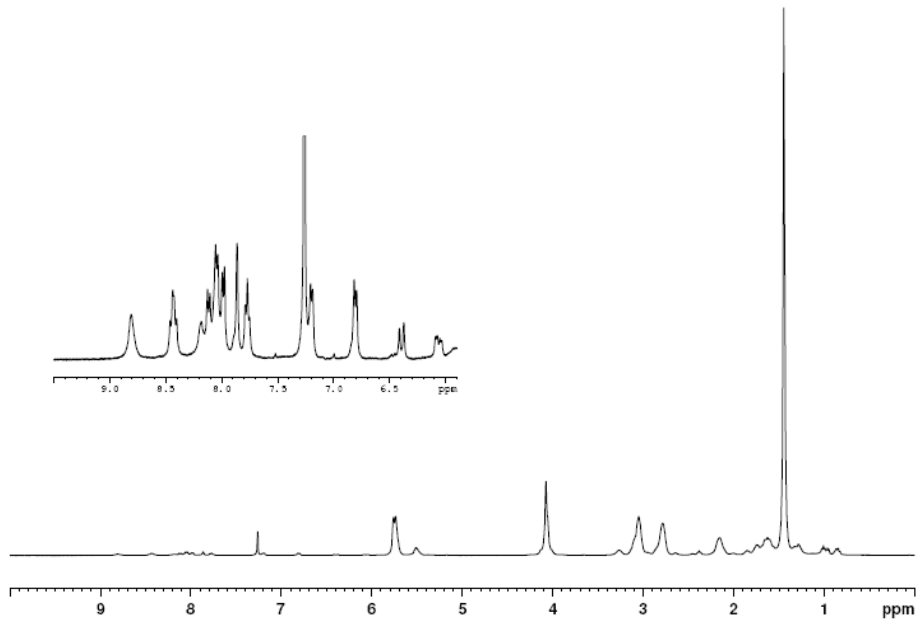

Figure C.2. ^{1}H NMR spectrum of **PB** in $CDCl_3$.

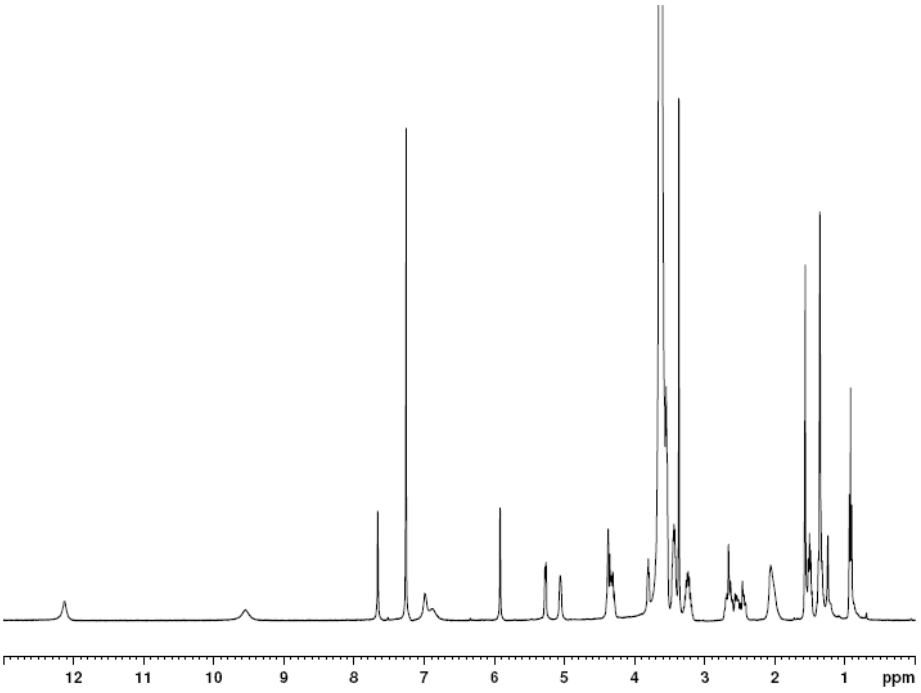

Figure C.3. ^{1}H NMR spectrum of **PC** in $CDCl_3$.